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[Intervention Review]

Selenium for preventing cancer

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ABSTRACT

Background

This review is the third update of the Cochrane review "Selenium for preventing cancer". Selenium is a naturally occurring element with both nutritional and toxicological properties. Higher selenium exposure and selenium supplements have been suggested to protect against several types of cancer.

Objectives

To gather and present evidence needed to address two research questions:

1. What is the aetiological relationship between selenium exposure and cancer risk in humans?
2. Describe the efficacy of selenium supplementation for cancer prevention in humans.

Search methods

We updated electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2), MEDLINE (Ovid, 2013 to January 2017, week 4), and Embase (2013 to 2017, week 6), as well as searches of clinical trial registries.

Selection criteria

We included randomised controlled trials (RCTs) and longitudinal observational studies that enrolled adult participants.

Data collection and analysis

We performed random-effects (RE) meta-analyses when two or more RCTs were available for a specific outcome. We conducted RE meta-analyses when five or more observational studies were available for a specific outcome. We assessed risk of bias in RCTs and in

observational studies using Cochrane's risk assessment tool and the Newcastle-Ottawa Scale, respectively. We considered in the primary analysis data pooled from RCTs with low risk of bias. We assessed the certainty of evidence by using the GRADE approach.

Main results

We included 83 studies in this updated review: two additional RCTs (10 in total) and a few additional trial reports for previously included studies. RCTs involved 27,232 participants allocated to either selenium supplements or placebo. For analyses of RCTs with low risk of bias, the summary risk ratio (RR) for any cancer incidence was 1.01 (95% confidence interval (CI) 0.93 to 1.10; 3 studies, 19,475 participants; high-certainty evidence). The RR for estimated cancer mortality was 1.02 (95% CI 0.80 to 1.30; 1 study, 17,448 participants). For the most frequently investigated site-specific cancers, investigators provided little evidence of any effect of selenium supplementation. Two RCTs with 19,009 participants indicated that colorectal cancer was unaffected by selenium administration (RR 0.99, 95% CI 0.69 to 1.43), as were non-melanoma skin cancer (RR 1.16, 95% CI 0.30 to 4.42; 2 studies, 2027 participants), lung cancer (RR 1.16, 95% CI 0.89 to 1.50; 2 studies, 19,009 participants), breast cancer (RR 2.04, 95% CI 0.44 to 9.55; 1 study, 802 participants), bladder cancer (RR 1.07, 95% CI 0.76 to 1.52; 2 studies, 19,009 participants), and prostate cancer (RR 1.01, 95% CI 0.90 to 1.14; 4 studies, 18,942 participants). Certainty of the evidence was high for all of these cancer sites, except for breast cancer, which was of moderate certainty owing to imprecision, and non-melanoma skin cancer, which we judged as moderate certainty owing to high heterogeneity. RCTs with low risk of bias suggested increased melanoma risk.

Results for most outcomes were similar when we included all RCTs in the meta-analysis, regardless of risk of bias. Selenium supplementation did not reduce overall cancer incidence (RR 0.99, 95% CI 0.86 to 1.14; 5 studies, 21,860 participants) nor mortality (RR 0.81, 95% CI 0.49 to 1.32; 2 studies, 18,698 participants). Summary RRs for site-specific cancers showed limited changes compared with estimates from high-quality studies alone, except for liver cancer, for which results were reversed.

In the largest trial, the Selenium and Vitamin E Cancer Trial, selenium supplementation increased risks of alopecia and dermatitis, and for participants with highest background selenium status, supplementation also increased risk of high-grade prostate cancer. RCTs showed a slightly increased risk of type 2 diabetes associated with supplementation. A hypothesis generated by the Nutritional Prevention of Cancer Trial - that individuals with low blood selenium levels could reduce their risk of cancer (particularly prostate cancer) by increasing selenium intake - has not been confirmed. As RCT participants have been overwhelmingly male (88%), we could not assess the potential influence of sex or gender.

We included 15 additional observational cohort studies (70 in total; over 2,360,000 participants). We found that lower cancer incidence (summary odds ratio (OR) 0.72, 95% CI 0.55 to 0.93; 7 studies, 76,239 participants) and lower cancer mortality (OR 0.76, 95% CI 0.59 to 0.97; 7 studies, 183,863 participants) were associated with the highest category of selenium exposure compared with the lowest. Cancer incidence was lower in men (OR 0.72, 95% CI 0.46 to 1.14, 4 studies, 29,365 men) than in women (OR 0.90, 95% CI 0.45 to 1.77, 2 studies, 18,244 women). Data show a decrease in risk of site-specific cancers for stomach, colorectal, lung, breast, bladder, and prostate cancers. However, these studies have major weaknesses due to study design, exposure misclassification, and potential unmeasured confounding due to lifestyle or nutritional factors covarying with selenium exposure beyond those taken into account in multi-variable analyses. In addition, no evidence of a dose-response relation between selenium status and cancer risk emerged. Certainty of evidence was very low for each outcome. Some studies suggested that genetic factors might modify the relation between selenium and cancer risk - an issue that merits further investigation.

Authors' conclusions

Well-designed and well-conducted RCTs have shown no beneficial effect of selenium supplements in reducing cancer risk (high certainty of evidence). Some RCTs have raised concerns by reporting a higher incidence of high-grade prostate cancer and type 2 diabetes in participants with selenium supplementation. No clear evidence of an influence of baseline participant selenium status on outcomes has emerged in these studies.

Observational longitudinal studies have shown an inverse association between selenium exposure and risk of some cancer types, but null and direct relations have also been reported, and no systematic pattern suggesting dose-response relations has emerged. These studies suffer from limitations inherent to the observational design, including exposure misclassification and unmeasured confounding.

Overall, there is no evidence to suggest that increasing selenium intake through diet or supplementation prevents cancer in humans. However, more research is needed to assess whether selenium may modify the risk of cancer in individuals with a specific genetic background or nutritional status, and to investigate possible differential effects of various forms of selenium.

PLAIN LANGUAGE SUMMARY

Selenium for preventing cancer

Review question

We reviewed the evidence investigating the relation between selenium intake and cancer prevention. This review updates the most recent Cochrane review on this topic (Vinceti 2014), which was an update of Dennert 2011.

Background

Selenium is a naturally occurring element that individuals are exposed to mainly through food consumption, although exposure can also occur through air, drinking water, and dietary supplements. Small amounts of selenium are essential for certain biological functions in humans, but slightly higher amounts can pose a toxicity risk, making selenium an element with a narrow, but as yet not well-defined, safe range of exposure. Selenium occurs in many different chemical forms with different biological activity. From the late 1960s, a few observational studies reported that people with high levels of selenium in their diet or in their body tissues had lower risk of cancer, and some laboratory studies showed that selenium could inhibit the growth of cancer cells. This led to widespread interest in selenium supplements and claims that taking such supplements could prevent cancer. Since that time, many more observational studies have been conducted to compare cancer rates among individuals with high and low selenium exposure. More recently, several randomised controlled trials designed to assess whether selenium supplementation can prevent cancer have been carried out. These trials played a major role in enhancing our understanding of the relation between selenium and cancer risk as a result of their stronger study design as compared with observational studies. The most recent trials in particular have shown high methodological quality and statistical power. Several trials focused on whether selenium could prevent prostate cancer.

Study characteristics

This review includes 10 trials in which adults were randomly assigned to receive selenium supplements or placebo, and 70 observational studies in which adults were followed over time to determine whether their baseline selenium status was associated with their risk of cancer. The evidence is current to January 2017.

Key results

All of the high-quality randomised trials reported no effect of selenium on reducing overall risk of cancer or risk of particular cancers, including the most investigated outcome - prostate cancer. Some trials unexpectedly suggested that selenium may increase risks of high-grade prostate cancer, type 2 diabetes, and dermatological abnormalities.

Observational studies have yielded inconsistent evidence of a possible effect of selenium exposure on cancer risk, with no evidence of a dose-response relation. When we pooled results of these studies, overall they suggested an inverse relation between cancer exposure and subsequent incidence of any cancer or some specific cancers, such as colon and prostate cancer. However, observational studies have major weaknesses. The selenium exposure status of participants could have been misclassified owing to limitations of the indicators of selenium exposure used, as well as to uncertainty regarding the particular selenium species contributing to overall exposure. In addition, unmeasured confounding from lifestyle or nutritional factors - a major and well-known source of bias in nutritional epidemiology studies of observational design - could have been present. Therefore, the internal validity of these studies is limited.

Currently, the hypothesis that increasing selenium intake may reduce cancer risk is not supported by epidemiological evidence. Additional research is needed to assess whether selenium may affect the risk of cancer in individuals with specific genetic backgrounds or nutritional status, and to determine how the various chemical forms of selenium compounds may have different effects on cancer risk.

Summary of findings for the main comparison. Highest compared with lowest selenium exposure for preventing cancer in randomised controlled studies with low risk of bias

Highest compared with lowest selenium exposure for preventing cancer in randomised controlled studies with low risk of bias

Patient or population: Participants in trials with low risk of bias
Setting: out-patient
Intervention: highest selenium exposure
Comparison: lowest selenium exposure

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Quality of the evidence (GRADE)	Comments
		Without highest	With highest	Difference		
Any cancer risk No. of participants: 19,475 (3 RCTs)	RR 1.01 (0.93 to 1.10)	Study population			⊕⊕⊕⊕ HIGH	SELECT study had the strongest influence on the effect estimate. The RR in all RCTs is 0.99 (95% CI 0.86 to 1.14).
		10.0%	10.1% (9.3 to 11.0)	0.1% more (0.7 fewer to 1 more)		
Cancer mortality risk No. of participants: 17,448 (1 RCT)	RR 1.02 (0.80 to 1.30)	Study population			⊕⊕⊕⊕ HIGH	The effect is led from the study SELECT. The RR in all RCTs is 0.81 (95% CI 0.49 to 1.32).
		1.4%	1.5% (1.1 to 1.9)	0.0% more (0.3 fewer to 0.4 more)		
Colorectal cancer risk No. of participants: 19,009 (2 RCTs)	RR 0.99 (0.69 to 1.43)	Study population			⊕⊕⊕⊕ HIGH	SELECT study had the strongest influence on the effect estimate. The RR in all RCTs is 0.74 (95% CI 0.41 to 1.33).
		0.7%	0.7% (0.5 to 1.0)	0.0% fewer (0.2 fewer to 0.3 more)		
Non-melanoma skin cancer risk No. of participants: 2027 (2 RCTs)	RR 1.16 (0.30 to 4.42)	Study population			⊕⊕⊕⊖ MODERATE[a]	Pooled estimate is imprecise owing to high heterogeneity. The RR in all RCTs is 1.23 (95% CI 0.73 to 2.08).
		2.9%	3.4% (0.9 to 12.9)	0.5% more (2 fewer to 10 more)		
Lung cancer risk No. of participants: 19,009 (2 RCTs)	RR 1.16 (0.89 to 1.50)	Study population			⊕⊕⊕⊕ HIGH	The RR in all RCTs is 1.03 (95% CI 0.78 to 1.37).
		1.0%	1.2% (0.9 to 1.5)	0.2% more (0.1 fewer to 0.5 more)		
Breast cancer risk No. of participants: 802	RR 2.04 (0.44 to 9.55)	Study population			⊕⊕⊕⊖ MODERATE[b]	The RR in all RCTs is 1.44 (95% CI 0.96 to 2.17).

(1 RCT)		0.7%	1.5% (0.3 to 7.0)	0.8% more (0.4 fewer to 6.3 more)		
Bladder cancer risk No. of participants: 19,009 (2 RCTs)	RR 1.07 (0.76 to 1.52)	Study population			⊕⊕⊕⊕ HIGH	SELECT study had the strongest influence on the effect estimate. The RR in all RCTs is 1.10 (95% CI 0.79 to 1.52).
		0.6%	0.7% (0.5 to 1.0)	0.0% fewer (0.2 fewer to 0.3 more)		
Prostate cancer risk No. of participants: 18,942 (4 RCTs)	RR 1.01 (0.90 to 1.14)	Study population			⊕⊕⊕⊕ HIGH	SELECT study had the strongest influence on the effect estimate. The RR in all RCTs is 0.91 (95% CI 0.75 to 1.12).
		5.4%	5.4% (4.8 to 6.1)	0.1% more (0.5 fewer to 0.8 more)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio; SELECT: Selenium and Vitamin E Cancer Prevention Trial.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for moderate heterogeneity ($tau^2 = 0.69$, $I^2 = 72\%$, $P = 0.06$) not explained.
[b]Downgraded one level owing to imprecision.

Summary of findings 2. Highest compared with lowest selenium exposure for preventing cancer in observational studies

Highest compared with lowest selenium exposure for preventing cancer in observational studies

Patient or population: Participants in non experimental cohort studies on selenium and cancer
Setting: out-patient
Intervention: highest selenium exposure
Comparison: lowest selenium exposure

Outcomes	Relative effect (95% CI)	Certainty of the evidence (GRADE)
Any cancer risk No. of participants: 76,239	OR 0.72 (0.55 to 0.93)	⊕⊖⊖⊖ VERY LOW[a]

(7 observational studies)		
Cancer mortality risk No. of participants: 183,863 (7 observational studies)	OR 0.76 (0.59 to 0.97)	⊕⊖⊖⊖ VERY LOW[a]
Colorectal cancer risk No. of participants: 712,746 (6 observational studies)	OR 0.82 (0.72 to 0.94)	⊕⊖⊖⊖ VERY LOW[a]
Lung cancer risk No. of participants: 371,067 (11 observational studies)	OR 0.82 (0.59 to 1.14)	⊕⊖⊖⊖ VERY LOW[a,b,c]
Breast cancer risk (women) No. of participants: 169,028 (8 observational studies)	OR 1.09 (0.87 to 1.37)	⊕⊖⊖⊖ VERY LOW[a,c]
Bladder cancer risk No. of participants: 279,100 (5 observational studies)	OR 0.67 (0.46 to 0.97)	⊕⊖⊖⊖ VERY LOW[a,c]
Prostate cancer risk No. of participants: 576,667 (21 observational studies)	OR 0.84 (0.75 to 0.95)	⊕⊖⊖⊖ VERY LOW[a,d]

CI: confidence interval; OR: odds ratio.

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level owing to risk of bias, which we deemed as serious because of inability to rule out unmeasured confounding, particularly from lifestyle or nutritional factors that might covary with selenium exposure beyond those factors taken into account in the multi-variable analyses.
[b]Downgraded one level for moderate heterogeneity ($tau^2 = 0.19$, $I^2 = 66\%$, $P = 0.0008$) not explained.
[c]Downgraded one level owing to imprecision.
[d]Downgraded one level owing to potential presence of publication bias suggested by the funnel plot.

BACKGROUND

This review is the third update of the Cochrane review titled "Selenium for preventing cancer" (Dennert 2011; Vinceti 2014).

Description of the condition

Cancer is a leading cause of death worldwide (WHO 2017). According to estimates of the International Agency for Cancer Research, 14.1 million people developed and 8.2 million died of cancer in 2012, and more than half of all new cases occurred in less developed regions of the world (IARC 2014).

The role of diet and nutrition in carcinogenesis and cancer prevention and the identification of nutritional factors and supplements with cancer preventive properties have been areas of active research for decades. Dietary factors that reduce cancer risk would clearly have major public health implications, but unfortunately, investigations into supplementation of various vitamins, trace elements, and other dietary constituents have typically yielded disappointing and even troubling results (Bjelakovic 2014; Fortmann 2013; Guallar 2013; Rocourt 2013; Schwingshackl 2017). Selenium is one of these nutritional factors (Vinceti 2013b).

Description of the intervention

The element selenium has received considerable attention as a potential cancer preventive agent, at least in populations with low intake. Selenium is recognised as nutritionally essential for humans, but it is toxic at levels slightly higher than those required for health, with a narrow and still not well-defined safe range of intake (Jablonska 2015a; Vinceti 2017a). Whether selenium provides various health benefits (including a cancer preventive effect) beyond its essential nutritional role continues to be a matter of debate (Allingstrup 2015; Bodnar 2012; Brigelius-Flohe 2017; Fortmann 2013; Karp 2013; Lippman 2009, in: SELECT 2009; Rayman 2012; Stranges 2010; Vinceti 2013a; Vinceti 2013b; Vinceti 2014a; Vinceti 2017a; Visser 2017; Wichman 2016). Humans usually ingest this trace element with crop, animal products, fish, and seafood, and sometimes in supplements (Hurst 2013a; Vinceti 2017a).

Chemical forms and concentrations of selenium in environmental matrices, foods, drinking water, and other sources of exposure vary considerably (Fairweather-Tait 2011). Selenium species can be classified into organically bound selenium forms (e.g. selenomethionine, selenocysteine) and inorganic forms (e.g. selenate, selenite) (Gammelgaard 2011; Weekley 2013). Organically bound selenium is present in the large number of selenoproteins identified in living organisms including humans, although the exact activity of some of these proteins remains to be identified (Brigelius-Flohe 2017; Hatfield 2014; Labunskyy 2014). Selenium yeast refers to a selenium-enriched yeast medium that usually contains selenium that is almost entirely organically bound, along with a high proportion of selenomethionine (Block 2004; Rayman 2004).

Recommended intake of selenium varies considerably among different regulatory agencies and scientific authorities (Vinceti 2017a). For example, the USA Institute of Medicine recommends daily intake of 55 µg/d for adults (Institute of Medicine 2009), whereas the World Health Organization (WHO) recommends amounts ranging from 25 to 34 µg/d, depending on age and sex (WHO 2004). More generally, international bodies have recommended amounts ranging from 25 to 70 µg/d for the adult population (Vinceti 2017a). The main reason for these differences in recommendations is the differing value and weight given to the proteomic effects of selenium, in particular whether or not selenoproteins sensitive to selenium supply must be up regulated to their maximal level, and whether any adverse health effects may arise at lower selenium intakes than those required to maximise selenoprotein expression (Jablonska 2015a; Vinceti 2017a). In addition, these standards generally do not take into account the chemical forms nor the source of selenium (diet, drinking water, air, etc.), despite established relevance of selenium speciation in addressing and assessing the health effects of this element (Vinceti 2013a; Vinceti 2013c; Weekley 2013; Vinceti 2017d).

To prevent adverse effects due to excessive selenium intake, the USA Institute of Medicine has set the tolerable upper intake level at 400 µg/d for adults (Office of Dietary Supplements 2009). However, recent epidemiological studies suggest overt human toxicity at lower intake levels (Lippman 2009, in: SELECT 2009; Stranges 2007; Vinceti 2017a), and lower upper safe levels have already been proposed (Tsubota-Utsugi 2012). In addition to the acute and chronic toxicity of high selenium exposure, possible harmful effects of long-term overexposure to lower dosages have been a matter of concern. However, these effects, such as those affecting the endocrine system, remain inadequately investigated (Vinceti 2001; Vinceti 2017a). Furthermore, evidence shows different biological activities of the various organic and inorganic forms of selenium (Hazane-Puch 2013; Mandrioli 2017; Vinceti 2013c; Vinceti 2017d; Weekley 2013), emphasising the need to better characterise the specific toxicological and nutritional properties of each selenium species in humans, in animals, and in the environment. Recent publications have questioned the adequacy of the current upper safe limit of intake (Jablonska 2015a; Jerome-Morais 2011; Marschall 2017; Morris 2013; Moyad 2012; Rocourt 2013; Sacco 2013; Vinceti 2013b; Vinceti 2017a) and have espoused the need to set different limits for the many different sources of organic and inorganic selenium. On the other hand, other investigators have described claims of widespread deficient intake of selenium (Hughes 2016).

Accurate estimation of selenium exposure in epidemiological studies presents several challenges. Individual exposure is typically assessed by using peripheral biomarkers of exposure, such as blood (usually plasma or serum) or nail concentrations, or by estimating dietary intake (Ashton 2009). Each of these methods has strengths and limitations and has had its validity questioned (Ashton 2009; Haldimann 1996; Vinceti 2013b). However, levels of selenium in peripheral biomarkers such as blood, toenail, and hair have been found to correlate to a moderate degree with dietary intake as assessed through self-reported consumption of supplements, food frequency questionnaires, and dietary records (Hurst 2013a; Longnecker 1996; Ovaskainen 1993; Pestitschek 2013; van den Brandt 1993). Stronger correlation has been seen at high intake levels (Morris 2013), although results of some studies were not consistent (Hunter 1990; Karita 2003; Satia 2006; Vinceti 2012). Assessment of selenium levels in specific body tissues is extremely complex, as these levels are not necessarily homogeneously reflected by all biomarkers because overall selenium exposure, as well as its chemical forms and other factors, influences distribution of the metalloid into various body compartments (Behne 1996; Behne 2010; Panter 1996; Vinceti 2000; Vinceti 2013c). For example,

circulating levels of some selenium species and of total selenium did not correlate with selenium content in the central nervous system as assessed by cerebrospinal fluid concentrations (Solovyev 2013; Vinceti 2013c), indicating both the tissue-specific significance of biomarkers and the importance of selenium speciation when the distribution of selenium in different body compartments, representing target organs for different diseases, is assessed.

Selenium levels found in human specimens and characterising intake of selenium show high global variability due to variation in factors such as dietary habits, food and soil selenium content, ethnicity, sex, age, individual metabolism, occupational exposure, exposure to coal and other sources of combustion, and smoking (Fairweather-Tait 2011; Haldimann 1996; Jablonska 2013; Rayman 2008). It is interesting to note that smoking tends to lower selenium biomarker concentrations, even though smoking is a source of selenium exposure - a phenomenon that might be related to increased excretion of the metalloid due to interaction with cadmium or other heavy metals (Jossa 1991; Kafai 2003). Globally, inconsistencies have been noted as to how these factors are associated with selenium levels (Haldimann 1996; Vinceti 2000). For example, selenium levels increased with age in women, but not in men, in the French SU.VI.M.AX cohort study (Arnaud 2007), but decreased with age in a female population in Ohio (Smith 2000); however, two studies in Switzerland and Austria could not find an association between age and selenium status among individuals of either sex (Burri 2008; Gundacker 2006). Sex-specific nutritional and health behaviours, as well as sex-specific differences in selenium metabolism and distribution across various body compartments, may contribute to observed discrepancies in selenium levels between men and women (Combs 2012; Rodriguez 1995).

How the intervention might work

The ability of selenium to counteract cancer cell growth as observed in a large number of laboratory studies may be due to its effects on DNA stability, cell proliferation, necrotic and apoptotic cell death in healthy and malignant cells, and/or regulation of oxidative stress and the immune system (for reviews, see: Fernandes 2015; Misra 2015). These abilities have suggested the possible utility of selenium compounds not only for cancer prevention but also for cancer therapy - a hypothesis that has been under active investigation (Bhattacharjee 2017; Shigemi 2017; Vinceti 2017b). Selenium may be involved in cancer prevention through the antioxidant properties of selenoproteins (Hatfield 2014; Labunskyy 2014), as well as through several other mechanisms (Fernandes 2015; Misra 2015; Weekley 2013). However, laboratory studies have shown that selenium can promote malignant cell transformation and progression (Chen 2000; Kandas 2009; Kasaikina 2013; National Toxicology Program 2011; Novoselov 2005; Rose 2014; Su 2005; Tsuji 2015), thus confirming the complex 'dual personality' of both this Janus-faced element and selenoproteins in preventing and promoting cancer (Hatfield 2014).

In addition, numerous epidemiological studies of observational design, which have reported an inverse association between selenium exposure and cancer risk (Vinceti 2017b), have provided support for the potential of selenium in cancer prevention. The first of these studies used an ecological study design (Schrauzer 1977; Shamberger 1969). These were followed by case-control and cohort observational studies, then by randomised trials, some of which received substantial attention from both the general public and the scientific community (Brinkman 2006; Fortmann 2013; Steinbrenner 2013; Vinceti 2013b). Some observational and experimental human studies have suggested that sex-related differences regarding effects of selenium on cancer risk, as well as differences in selenium tissue distribution, tumour biology, and other factors, may explain the possibly greater beneficial effect of selenium for men than for women in the earliest studies (NPCT 2002; Waters 2004).

Why it is important to do this review

Findings of laboratory studies and early epidemiological studies have led to the suggestion that selenium may be involved in central anticarcinogenic processes. This has resulted in widespread marketing of selenium supplements with associated health claims, particularly claims for prevention of cancer (Dennert 2011; Vinceti 2013b), as well as prevention of cardiovascular disease (Rees 2013). However, accumulating evidence suggests that this early optimism may have been unwarranted (Kryscio 2017; Lance 2017; Lu 2016; Ramamoorthy 2015; Vinceti 2017a; Vinceti 2017b). In particular, additional evidence on selenium and cancer risk gathered by high-quality randomised controlled trials (RCTs) has become available in recent years, and a few observational studies have been published, thus justifying an update on epidemiological evidence regarding selenium exposure and cancer risk. We undertook this updated review to perform a comprehensive synthesis of current epidemiological evidence.

OBJECTIVES

To gather and present evidence needed to address two research questions:.

1. What is the aetiological relationship between selenium exposure and cancer risk in humans?
2. Which is the efficacy of selenium supplementation for cancer prevention in humans?

METHODS

Criteria for considering studies for this review

Types of studies

We included published randomised controlled trials (RCTs) and observational studies of longitudinal design (i.e. cohort studies and nested case-control studies), irrespective of publication status or language, provided they were published in extenso. We also included conference abstracts in this review when we were able to retrieve them through citation chasing (Vinceti 2017c).

Types of participants

Adult participants (18 years of age and older).

Types of interventions

We considered RCTs for inclusion if they used selenium supplementation at any dose or route of administration for a minimum of four weeks versus placebo or no intervention. We excluded trials using selenium supplementation as part of a multi-component preparation if they did not include a study arm using selenium monotherapy supplementation.

We considered prospective observational studies (cohort studies and cohort-nested and nested case-control studies) for inclusion if they assessed baseline exposure to selenium in apparently cancer-free individuals as a biomarker of selenium status or as dietary assessment of selenium intake at study entry, provided that such assessment was based on exposure categories - not just on continuous values.

Types of outcome measures

We systematically analysed all (primary and secondary) outcomes.

Primary outcomes

1. Incidence of any cancer and of site-specific cancers, assessed as proportions of participants developing cancers during the study period.
2. Mortality from any cancer and from site-specific cancer, assessed as proportions of participants dying from cancers during the study period.

Secondary outcomes

1. Incidence of selected adverse effects, assessed as proportions of participants developing adverse health conditions (RCTs only).

Search methods for identification of studies

Using the search strategies described previously, we conducted updated electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2), MEDLINE (Ovid, 2013 to January 2017, week 4), Embase (2013 to 2017, week 6), CancerLit (cancer literature database; February 2004), and Clinical Contents in Medicine (CCMed; February 2011). We conducted the initial search in 2004 and updated searches in July 2007, January 2009, October 2009, February 2011, February 2013, and February 2017. As MEDLINE now includes the journals indexed in CancerLit no further searches of this database were made after 2004.

We also searched the following online clinical trials databases as in the previous review Vinceti 2014.

1. Clinical Trials of the American Cancer Society (http://www.cancer.gov; February 2011).
2. metaRegister of Controlled Trials (http://www.controlled-trials.com; February 2011).
3. German Cancer Study Register (http://www.studien.de; February 2011).
4. System for Information on Grey Literature in Europe (SIGLE) (February 2004, discontinued in 2005).
5. International Standard Registered Clinical/Social Study Number (ISRCTN) registry (http://www.isrctn.com; February 2017).
6. ClinicalTrials.gov registry (https://clinicaltrials.gov; February 2017).

We have provided the search strategies in Appendix 1.

Data collection and analysis

Selection of studies

Two review authors independently checked all electronic search results for eligibility. When search results could not be rejected with certainty on the basis of title, abstract, or both, we obtained full-text material.

We scanned bibliographies of papers retrieved using the described search strategy to identify additional studies. When additional information was needed, we contacted the correspondent authors of included studies; we also asked investigators for information about unpublished RCTs.

Two review authors (MV and TF) independently applied the inclusion and exclusion criteria, if necessary with the assistance of a translator. We resolved disagreements by discussion and with involvement of a third review author (CDG).

Data extraction and management

We used piloted extraction forms for epidemiological studies and RCTs to document data from the original material and to assess the quality of studies. One review author (TF) extracted data, and two review authors (MV and CDG) checked extracted data for discrepancies, which the three review authors (TF, MV, and CDG) then discussed. If several reports from the same study were available, we considered as primary publications studies reporting the entire period of follow-up with active selenium supplementation, when available, but we also extracted study details and results available from other publications, if they were not reported in the primary study reference.

For comparison of selenium exposure measured in serum and plasma specimens, we converted all data into the unit µg/L. We converted results provided as ppm (parts per million) or µg/g by using the factor 1.026 g/mL (density of blood plasma), and we converted data provided as µmol/L using the factor 78.96 (atomic weight of selenium).

For inclusion, prospective observational studies had to report estimates of risk ratio (RR), such as hazard ratio (HR) or odds ratio (OR), for various selenium category exposure levels. We did not include in the analysis studies reporting only the RR for a one-unit increase in selenium exposure on a continuous scale.

Assessment of risk of bias in included studies

Randomised controlled trials

We categorised generation of allocation sequence, allocation concealment, blinding, and completeness of outcome data as adequate (low risk of bias), inadequate (high risk of bias), or unclear, according to the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* and Higgins et al (Higgins 2011a; Higgins 2011b). We considered these four items to be key domains for risk of bias assessment. We considered studies that were categorised as 'adequate' in all four domains to have low risk of bias; and studies with 'inadequate' procedures in one or more key domains to have high risk of bias. We considered studies with 'unclear' procedures in one or more key domains to have unclear risk of bias.

We assessed fulfilment of ethical standards as follows.

1. Was informed consent obtained from participants? (yes/no/unclear).
2. Was approval obtained from an ethics board? (yes/no/unclear).

Observational studies

We assessed risk of bias in observational studies by using assessment forms adapted from the Newcastle-Ottawa Quality

Assessment Scale (NOS) for cohort and case-control studies (Wells 2004). We used the NOS form for cohort studies for all included observational studies, and the NOS case-control form for nested case-control studies. Both forms must be adapted a priori for use in a systematic review according to the research questions examined and the review topic explored. The NOS uses a star system by which studies are judged on key domains pertaining to selection and comparability of study groups, ascertainment of exposure and outcomes, and duration of follow-up. For each domain, we assigned either a 'star' or 'no star', with a star indicating that study design element was considered adequate and was less likely to introduce bias. A study could receive a maximum of nine stars during the cohort assessment (Appendix 2) and nine stars during assessment of the case-control portion (Appendix 3).

The risk of bias assessment was based on data provided in the included publications. When relevant data for such assessment were missing, we tried to contact the trial authors to ask that they provide them.

Measures of treatment effect

This review includes only the binary outcome of cancer diagnosis (i.e. cancer incidence) or death from cancer (i.e. cancer mortality), or a combination of both. We used the term 'cancer risk' in this paper as a generic term that refers generally to cancer incidence, cancer mortality, and combined incidence/mortality data.

For RCTs, we used risk ratios (RRs) and their 95% confidence intervals (95% CIs). When hazard ratios (HRs) rather than RRs were reported in the original study, we reported individual study results as HRs along with their 95% CIs.

For observational studies, we used odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) and their corresponding 95% CIs as measures of association between cancer risk and selenium exposure. When adjusted estimates were reported, we used those with the most extensive covariate adjustment reported in the publication.

Dealing with missing data

When data were missing or when discrepancies in study publications were found, we tried to contact the study investigators to request further information. In most cases, review authors resolved the issues through collaboration; when no reply came from the trial authors, we did not use the corresponding data.

When a study combined subgroups, only some of which fulfilled our eligibility criteria (e.g. including individuals not affected by cancer), or did not report enough information to be included in this update, we systematically contacted trial authors to ask that they provide the additional information. We are grateful to the several trial authors who agreed to provide these additional data.

Assessment of heterogeneity

We used the Chi^2 test for heterogeneity and I^2 statistics to quantify heterogeneity of study results (Higgins 2003).

Assessment of reporting biases

We evaluated the possibility of reporting bias by using funnel plots.

Data synthesis

We performed data synthesis and analysis separately for RCTs and observational studies.

For RCTs, we performed meta-analyses for all cancers or site-specific cancers when at least two trials could provide data, given their fundamental importance in epidemiological research. When more than one publication from the same trial was available and reported different periods of follow-up for the same cancer site, we included in the meta-analysis only the longest period of follow-up, provided that the experimental protocol was ongoing at the time of follow-up (i.e. that selenium supplementation was still actively supplied). We assessed the stability of effect estimates through their 95% or 99% confidence intervals. We included lack of precision of effect estimates among the factors used to downgrade the certainty (quality) of evidence generated by studies via the GRADE approach (www.gradeworkinggroup.org). For RCTs, we considered pooled data from studies with low risk of bias as the primary analysis.

For observational studies, the minimum number of studies for inclusion in the meta-analysis was five, as in the previous version of the review. We applied this latter restriction not only to limit the number of analyses performed, but also because results were largely expected to be heterogeneous, and heterogeneity cannot be described and quantified adequately if too few studies are available (Higgins 2009).

We calculated RRs and 95% CIs using numbers of participants and cases when these were provided in the publication and the meta-analysis tool provided by Review Manager 2014; otherwise, we used RRs reported in the original publication, and, in particular, we selected RRs with the least adjustment for potential confounders. We used the same approach in calculating the RRs of adverse outcomes. We conducted random-effects meta-analyses of summary statistics for both observational studies and RCTs. For observational studies, we used the OR or RR comparing highest and lowest selenium exposure categories. We entered effect estimates as the natural logarithm of the OR or RR, and we used the squared standard error of the natural logarithm of the OR or RR as a weight. We calculated the latter from reported upper and lower boundaries of the 95% CI of the OR or RR. If a 95% CI was not reported, we used the total number of cases and the total number of controls, as well as the number of categories of selenium exposure, to estimate numbers of cases and controls per exposure category. We then used the standard normal approximation formula to calculate the standard error of the OR, comparing the highest versus the lowest exposure category (lnOR = (1/a + 1/b + 1/c + 1/d), where a, b, c, and d are the four counts needed to calculate the OR via (a*d)/(b*c)). For experimental studies, we computed the RR of cancer in the intervention group compared with that in the placebo group. For one study, which included more than one treatment (Algotar 2013), we used only results for the lowest dose (200 µg/d) for consistency with other studies. We conducted all meta-analyses by using Review Manager 5.3.5 and Stata-15 statistical tools. To do this, we copied logarithmic data for the OR and the standard error from Stata into Review Manager, then double-checked results for errors.

Subgroup analysis and investigation of heterogeneity

We carried out a subgroup meta-analysis for high-quality RCTs while excluding from analysis all trials showing high or uncertain risk of bias.

For observational studies, we used sex-disaggregated data from mixed-sex studies, together with data from single-sex cohorts, to conduct subgroup analyses by sex. We also carried out subgroup analyses specific for baseline selenium status. For these analyses, we assessed the evidence for an exposure-response relation by examining studies in ascending order from the bottom category of selenium exposure and by examining differences between highest and lowest exposure categories.

Sensitivity analysis

For RCTs, we considered risk estimates derived by pooling data from all studies, regardless of risk of bias, as part of a sensitivity analysis.

For observational studies, we conducted sensitivity analyses to assess the effects of different methods used to assess selenium status (i.e. assessment of intake via dietary assessment methods or measurement of exposure biomarkers such as blood and toenail selenium content).

'Summary of findings' table

We presented the overall certainty (quality) of evidence for the risk of any cancer, cancer mortality, colorectal cancer, lung cancer, non-melanoma skin cancer, breast cancer, bladder cancer, and prostate cancer from RCTs with low risk of bias. We also presented the overall certainty of evidence for these outcomes from observational studies, with the exception of non-melanoma skin cancer.

We evaluated the overall certainty of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADE Working Group 2004), which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results (Langendam 2013). We created two 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2) while adhering to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) and using GRADEpro GDT We used the GRADE checklist and GRADE Working Group certainty (quality) of evidence definitions (Meader 2014), as follows.

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

When possible, for each outcome in RCTs, we based the assumed risk in the control group on the proportion of events in the included studies. In accordance with GRADE methodological criteria, we based our assessment of the certainty (quality) of evidence on RCTs with low risk of bias (Guyatt 2011). We downgraded the evidence from 'high' quality by one level for serious (or by two levels for very serious) concerns regarding each of the validity issues.

RESULTS

Description of studies

Citation style: Please note that we reference the sources of relevant information in a certain way to enhance traceability of our results for interested readers. When the source of information is not the primary publication of an included study, we also reference the specific publication of interest. For example "Hakama 1990, in: Knekt 1990" indicates that the cited paper is "Hakama 1990" as part of the mentioned study.

We could not access three full-text theses published in the United States (Coates 1987, in: Coates 1988; Menkes 1986a, in: Menkes 1986; Schober 1986, in: Menkes 1986). However, later journal publications were available, and we included them in this review as main study publications (Coates 1988, in: Coates 1988; Menkes 1986b, in: Menkes 1986; Schober 1987, in: Menkes 1986). Thus we considered retrieval of the full-text theses to be unnecessary.

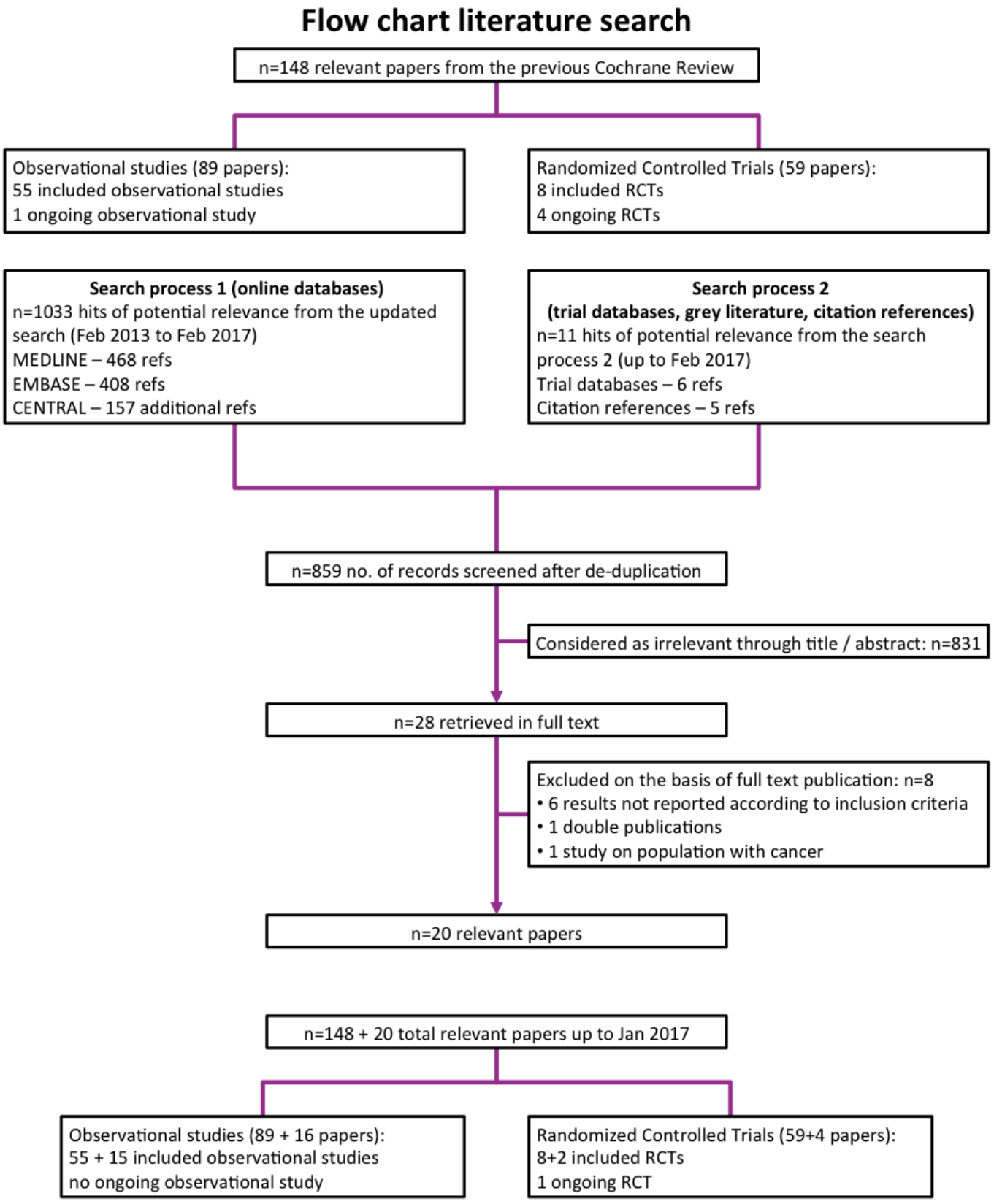
Results of the search

In the previous Cochrane review, of 4082 hits of potential relevance, we retrieved 268 publications in full text. Of these, we considered 137 papers as relevant (see the flow chart of the literature search in Dennert 2011).

In our first updated search, after we excluded internal duplicates and duplicates against the database of the literature search conducted in January 2011, we retrieved 766 hits. Of these, we excluded 744 references as clearly irrelevant on the basis of title and abstract review (see the flow chart of the literature search in Vinceti 2014).

In the second updated search process, conducted in February 2017, including online database searches and searches within grey literature, study references, and trial databases, we identified 859 new hits after de-duplication. Of these, we excluded 831 references as clearly irrelevant on the basis of the title and abstract review (see the flow chart of the literature search in Figure 1). We considered the remaining 28 publications of possible relevance and re-evaluated and retrieved them in full text from this updated search. Upon further review, we considered 20 of these publications relevant.

Figure 1. Flow chart.



Included studies

In total, from the previous Cochrane review and from our updates, we identified 168 papers for inclusion in this review: 105 papers referred to 70 completed observational studies, and 63 papers referred to one ongoing and 10 completed RCTs (Figure 1). (The previous version of the review was based on 148 papers; 89 referred to one ongoing and 55 completed observational studies, and 59 papers referred to four ongoing and eight completed RCTs.)

We have provided a detailed description of the included studies in the Characteristics of included studies table.

Randomised controlled trials

We included in this review 11 randomised controlled trials (RCTs) with a total of 44,743 participants (94% men). All used parallel-group designs with two arms (Dreno 2007; Karp 2013; Li 2000; Lubinski 2011; Marshall 2011; NPCT 2002; Reid 2008; Yu 1991; Yu 1997), three arms (Algotar 2013), or four arms (SELECT 2009). Three were conducted in China (Li 2000; Yu 1991; Yu 1997), four in the United States (Karp 2013; Marshall 2011; NPCT 2002; Reid 2008), one in the United States/New Zealand (Algotar 2013), one in the United States/Canada/Puerto Rico (SELECT 2009), and one in Europe (Lubinski 2011).

Investigators administered selenium supplements and placebos daily. As an active intervention, trials used selenium 200 µg/d (Dreno 2007; Karp 2013; Marshall 2011; NPCT 2002; Yu 1991; Yu 1997), or 400 µg/d (Reid 2008), in the form of selenised yeast tablets, composed almost entirely of organic selenium and particularly of selenomethionine (Block 2004). Algotar 2013 used 200 µg and 400 µg as different arms. Li 2000 used 500 µg sodium selenite, and SELECT 2009 used 200 µg/d of selenomethionine. Lubinski 2011 used 250 µg/d of inorganic selenite.

Three Chinese trials investigated the preventive efficacy of selenium supplementation against primary liver cancer for different high-risk populations. Participants were carriers of the hepatitis B surface antigen (HBs-Ag) with normal liver function, or they were first-degree relatives of patients with liver cancer. Two trials used selenised yeast (Yu 1991; Yu 1997), and one used sodium selenite (Li 2000).

The Nutritional Prevention of Cancer Trial (NPCT) investigated the influence of selenium on the development of non-melanoma skin cancer (basal and squamous cell carcinoma) in a population considered at high risk of the disease, namely, patients with a history of non-melanoma skin cancer (NPCT 2002). Participants consisted of 1312 men and women from the eastern United States 18 to 80 years of age, with a history of two or more basal cell carcinomas or of one squamous cell carcinoma. Investigators reported RR estimates for basal cell carcinoma, squamous cell carcinoma, and overall non-melanoma skin cancer for two periods of follow-up: an intermediate study period (from 15 September 1983 to 31 December 1993: Clark 1996, in: NPCT 2002), and the entire blinded intervention period (from 15 September 1983 to 31 January 1996: Duffield-Lillico 2002 for secondary outcomes; Duffield-Lillico 2003a for the primary outcome, i.e. non-melanoma skin cancer; and Duffield-Lillico 2003b for an in-depth analysis of prostate cancer risk; see NPCT 2002). In the present analysis, we used only final reports concerning the entire period of blinded follow-up, which was characterised by active administration of selenium supplements.

In 1990, NPCT 2002 identified additional secondary endpoints post hoc (i.e. total cancer mortality; total cancer incidence; incidence of lung, prostate, and colorectal cancers). Trial publications also reported incidences of female breast cancer, bladder cancer, oesophageal cancer, melanoma, haematological cancer, and cancers of the head and neck (NPCT 2002).

A substudy of the NPCT investigated the efficacy of a higher selenium dose, supplied as selenised yeast orally, for prevention of non-melanoma skin cancer at one of the NPCT study sites (Reid 2008). Study design was similar to that of the NPCT study, except that investigators randomly assigned 423 participants at this site to placebo or intervention with 400 µg/d of selenium. Reid 2008 also reported the incidence of internal cancers.

Dreno 2007 evaluated the incidence of skin cancer as a secondary outcome in a group of 184 organ transplant recipients who received 200 µg/d of selenium for three years, then were followed up for an additional two years. In this multi-centre, randomised, placebo-controlled trial, investigators monitored 91 selenium-supplemented participants and 93 non-supplemented participants for development of both non-malignant (warts and various keratoses) and malignant skin lesions.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT 2009) investigated the effect of selenium as L-selenomethionine and/or vitamin E supplementation in men of diverse ethnic backgrounds against the development of prostate cancer and other 'secondary' outcomes (i.e. risk of all cancers, lung cancer, colorectal cancer, and bladder cancer). This study was a very large phase 3 randomised, placebo-controlled trial, activated in June 2001 and originally designed for a 7- to 12-year period of follow-up, carried out at 427 sites in the United States, Canada, and Puerto Rico. However, the independent Data and Safety Monitoring Committee (DSMC) recommended on 15 September 2008, discontinuation of study supplements based on absence of benefit from vitamin E or selenium and no possibility of benefit to the planned degree with additional follow-up (SELECT 2009). The Committee also expressed concern about increased prostate cancer risk among vitamin E–treated participants and increased diabetes risk among selenium-supplemented participants (SELECT 2009) (RR 1.07, 99% CI 0.94 to 1.22). Therefore, investigators discontinued administration of these supplements on 23 October 2008, in spite of the planned supplementation period of 12 years. Results of SELECT are based on follow-up provided at the end of the blinded supplementation period, which included 117,660 person-years of follow-up - not on an extended period of follow-up, which encompassed an additional 32 months of surveillance (144,846 person-years in total) after the end of the supplementation period (Klein 2011, in: SELECT 2009). Endpoints were prostate cancer (the 'primary' endpoint) and colorectal cancer, lung cancer, all other cancers, and all cancers overall. A subsequent study from SELECT also evaluated the risk of bladder cancer, adding to standard follow-up an additional post supplementation period of 32 months (Lotan 2012, in: SELECT 2009).

Three phase III trials published in 2011 - Marshall 2011 - and in 2013 - Algotar 2013; Karp 2013 - also evaluated the effect of selenium supplementation on prostate cancer. In Marshall 2011 (trial code SWOG S9917), investigators randomly assigned 423 men with high-grade prostatic intraepithelial neoplasia, and therefore considered to be at very high risk of prostate cancer, to selenium (200 µg/d as selenomethionine) or placebo. Algotar 2013 evaluated whether

supplementation with 200 or 400 µg/d of selenium as selenised yeast reduced the risk of prostate cancer among men at high risk of the disease, based on a prostate-specific antigen (PSA) level exceeding 4 ng/L, suspicious digital rectal examination. and PSA velocity greater than 0.75 ng/mL/y. This trial, called the Negative Biopsy Trial (NBT), followed study participants in the United States (where both supplementation and follow-up were completed for such period) for five years, and in New Zealand for no longer than three years, and was discontinued after an external DSMC issued a recommendation to stop the trial. Karp 2013 investigated the effect of supplementation of 200 µg/d selenium as selenised yeast in 1561 individuals with resected stage I non–small-cell lung cancer (trial code ECOG 5597). The primary outcome was the incidence of second primary tumours. Investigators enrolled both men and women in the study and investigated all cancer types and a few major side effects during follow-up. Follow-up included the period of active supplementation and some additional follow-up after the trial anticipated discontinuation. This decision was made by the trial DSMC, which, on October 21, 2009, reviewed the first planned interim analysis of the primary endpoint and recommended that the study should be terminated for futility. Based on that DSMC recommendation, on November 5, 2009, accrual for the Eastern Cooperative Oncology Group (ECOG) trial was interrupted, and all current participants were invited to discontinue selenium/placebo tablets and were monitored only for follow-up of cancer incidence and survival. In accordance with recommendations by the trial DSMC concerning possible adverse effects of selenium supplementation, the incidence of basal and squamous cell skin cancers, as well as type 2 diabetes, was monitored. The main paper reported follow-up until June 2011 (Karp 2013), and results for only second primary lung tumours were updated as of January 2014, including a longer post supplementation period of follow-up (Pillai 2014, in: Karp 2013).

Investigators conducted a trial in Poland that included a female population of carriers of a breast cancer-related mutation, *BRCA1* (Lubinski 2011). Trial authors randomised 1135 women carrying that mutation to 250 µg/d of selenium in its inorganic tetravalent form (selenite), or to placebo, in a double-blind trial. Median follow-up lasted 35 months (ranging from 6 to 62 months), and final analysis was based on 105 incident cases diagnosed during follow-up - 60 cases in the selenium-supplemented arm and 45 cases in the placebo arm.

Observational studies

We included in this review 70 completed observational studies. Forty-five studies were nested case-control studies, the others were subcohort-controlled or cohort studies, and one study used a cohort together with a nested case-control design. Subcohort-controlled studies used (random) samples of the cohort as controls. The original papers were published between 1983 and 2017. Eight studies were conducted in Asia (China, Iran, Japan, and Taiwan), one in Australia, 30 in Europe (Belgium, Denmark, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, Channel Islands, Finland, France, and UK), 30 in the United States, and one in Canada. Overall, studies included more than 2,300,000 participants. Study populations in Europe made up 42.9%, North America 44.3%, Asia 11.4%, and Australia 1.4% of all study participants. The median size of study populations was 11,457. Forty-one studies included men and women, one did not report sex, 22 included only men, and six included only women. Eleven studies with mixed-sex populations reported results stratified by sex. Study populations were derived from 55 different cohorts. Twenty-four cohorts were non-randomly recruited (e.g. included volunteers), and 31 cohorts consisted of a random sample of the population of interest. Fifty-two studies reported mean or median age, 12 studies reported only age range, and six studies did not report this information on study participants. Most studies included adults older than 40 years of age.

Sixteen studies investigated nutritional and/or supplemental selenium intake by using food frequency questionnaires or interviews. Fifty-four studies assessed biochemical selenium status whereby:

1. 9 used toenail specimens;
2. 14 used plasma specimens;
3. 29 used serum specimens;
4. 1 used both serum and plasma specimens; and
5. 1 measured both serum selenium levels and intake.

The mean follow-up period lasted up to three years in five studies, and longer than three years in the remaining studies. Generally, study authors grouped cases according to the version of the International Classification of Diseases (ICD) that was up-to-date at the inception of the cohort observation. The level of disaggregation of data varied markedly between studies. Although some studies reported cancer risk according to organ system (e.g. urinary tract, respiratory tract), others reported cancer risk for one or two organs (e.g. female breast, urinary bladder). Only in the case of skin cancer did studies also differentiate according to histological type (e.g. melanoma, basal cell carcinoma).

For the following outcomes, we included five or more studies in the review and meta-analysed observational data.

1. Any cancer (16 studies).
2. Female breast cancer (8 studies).
3. Urinary bladder cancer (6 studies).
4. Lung cancer (15 studies).
5. Prostate cancer (21 studies).
6. Stomach cancer (5 studies).
7. Colorectal cancer (6 studies) and colon cancer (5 studies).

Goyal 2013 updated results of Bleys 2008, which reported longer follow-up for the same population.

Table 1 provides an overview of the studies examining each outcome. Five studies provided data for the group of 'other' cancers, which encompassed any type of cancer not reported separately in study publications. The definition of 'other' cancers varied between studies, including rare cancers but also cancers of unknown origin. We have mentioned results of studies within the category 'other cancers' for the sake of completeness; however, because of the diversity of outcomes, we have not included these results in further analysis or discussion of this review.

Excluded studies

Of 28 potentially relevant papers retrieved in the updated search, eight papers did not fulfil the inclusion criteria. We rejected six of these publications as investigators did not report results according to inclusion criteria; one paper because trial authors reported duplicated data from an already included study; and another paper

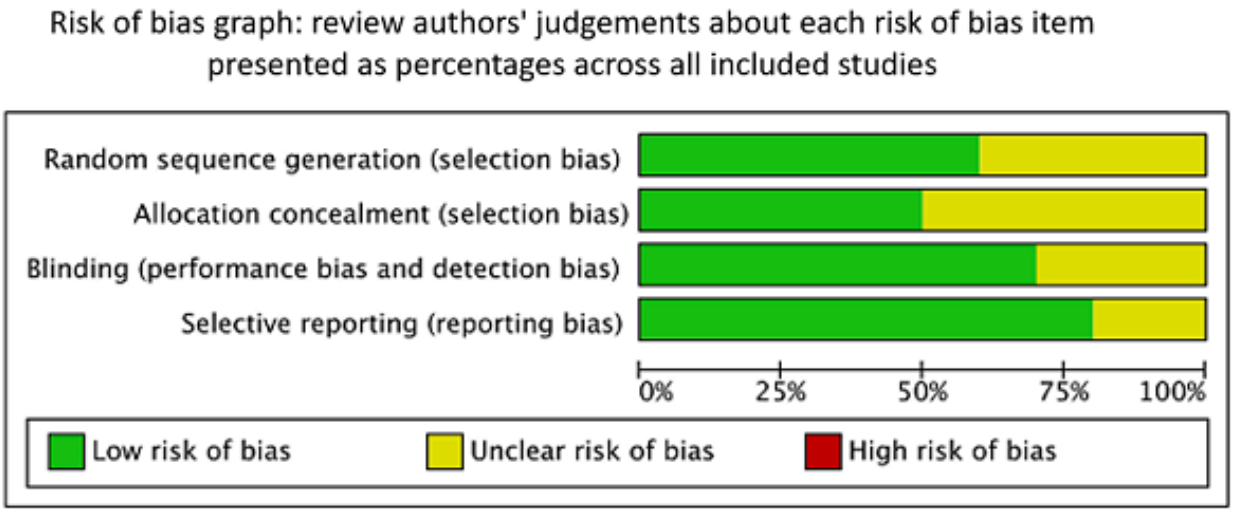
because the trial was carried out in patients with cancer. The Characteristics of excluded studies table describes the reasons for exclusion of trials from the previous Cochrane review and from this update.

Risk of bias in included studies

Randomised controlled trials

We assessed risk of bias of the included RCTs according to Cochrane criteria (Higgins 2011a; Higgins 2011b). We presented judgements about each risk of bias item as percentages across all included RCTs, and we provided a summary of the risk of bias assessment in Figure 2. We provided details on the judgement for each RCT and the reason for that judgement in Characteristics of included studies.

Figure 2. Review authors' judgements about each risk of bias item presented as percentages across all included RCTs and summary of review authors' judgements about each risk of bias item for the included RCTs.



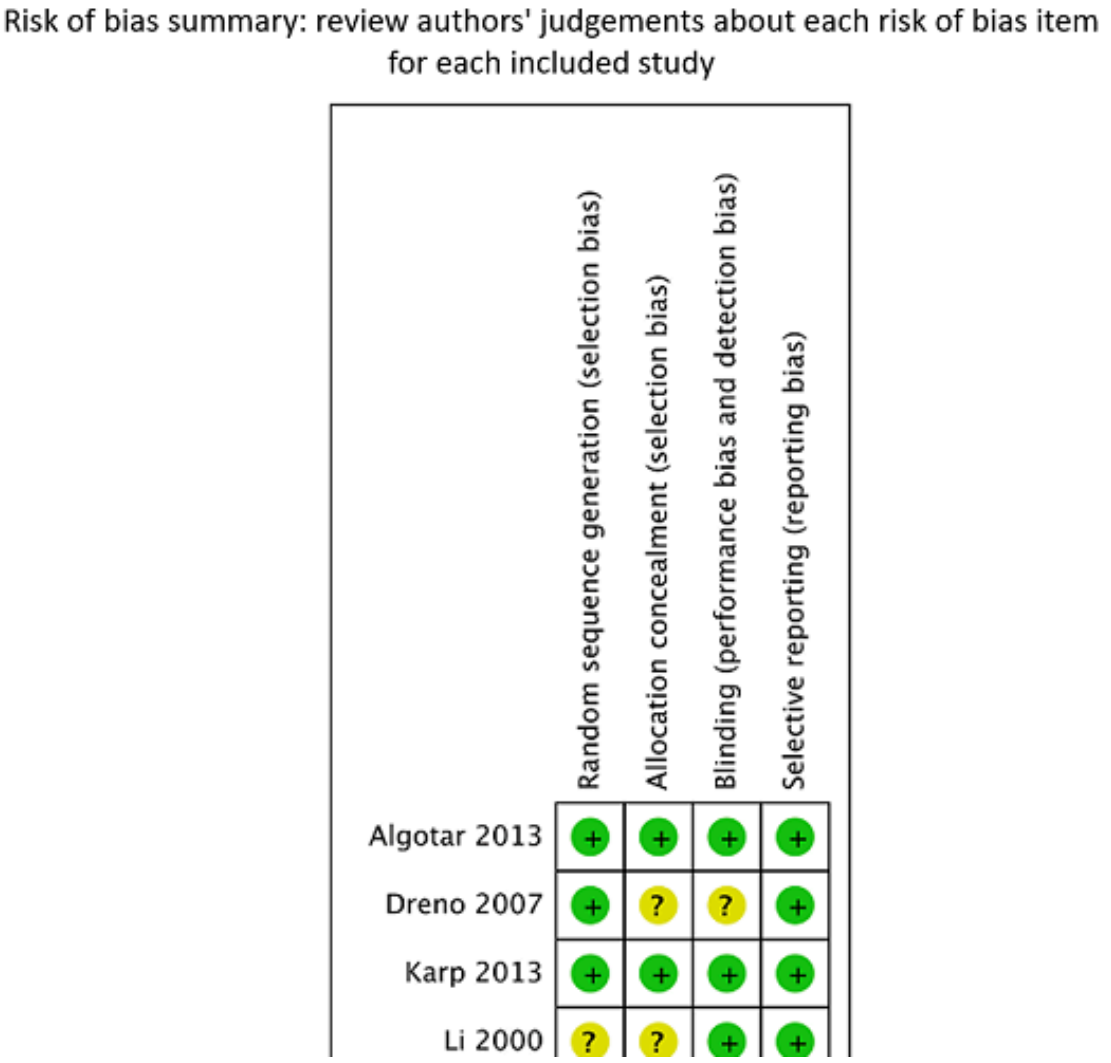
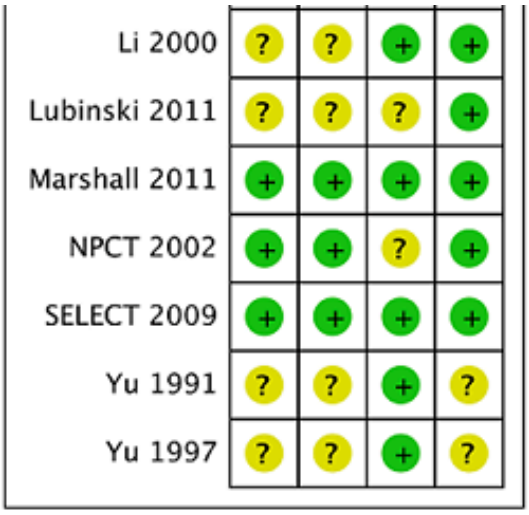


Figure 2. (Continued)



We considered all three trials on liver cancer risk (Li 2000; Yu 1991; Yu 1997), as well as the trial on breast cancer (Lubinski 2011), to have unclear risk of bias. These trials did not report generation of allocation sequence and allocation concealment. One study mentioned that the dropout rate was similar in intervention and control groups; the remaining three studies did not report the completeness of outcome data. We judged blinding as adequate in three studies, as investigators reported the use of placebo supplements. We inferred from this procedure that at least the study participants and the physicians directly involved were blinded towards treatment status.

In addition, it is unclear whether Li 2000 was an individually randomised controlled trial. Study investigators used the phrase "randomisation based on the residence area" and did not describe the randomisation procedure any further. As participants were recruited from 17 villages, these villages - not individual participants - may have been randomly assigned to intervention and control groups. However, we could not make contact with study investigators to clarify these questions. Randomisation of villages instead of individuals could have introduced bias into the study results, as the incidence of liver cancer is known to differ between geographical areas as a result of lifestyle and environmental factors.

It has been found that RCTs with inadequate or unclear allocation concealment, especially those with subjective outcomes, may overestimate the benefit of interventions (Pildal 2007; Wood 2008). All three RCTs on liver cancer did not report follow-up and case detection procedures, so the influence of subjective factors on case detection, such as interpretation of bodily symptoms as triggers of further diagnostic tests, is unknown. Although we judged blinding as 'adequate' in all three liver cancer trials, we do not know whether blinding was successful in practice for participants, healthcare providers, and outcome assessors.

These uncertainties about study methods seriously weaken our confidence in reported RCT results on liver cancer risk.

We considered Algotar 2013, Karp 2013, Marshall 2011, and SELECT 2009 to have low risk of bias because they reported adequate generation of allocation sequence, allocation concealment, blinding, and completeness of outcome data.

We judged Dreno 2007 and Duffield-Lillico 2002 to 2003, in: NPCT 2002 to have unclear risk of bias. Dreno 2007 provided unclear generation of allocation sequence, allocation concealment, and blinding; only completeness of outcome data was adequate. We considered NPCT to be at unclear risk of bias because of exposure-related detection bias for its primary outcome, as the percentage of study participants with an abnormal PSA (> 4 ng/mL) who underwent biopsy varied according to selenium treatment group, at 35% in the placebo group and 14% in the selenium-treated group (Duffield-Lillico 2003b, in: NPCT 2002; Marshall 2011). As reported by the trial authors themselves in analyses stratified by baseline selenium concentration, the difference was greatest among participants in the lowest tertile, in whom the inverse association between selenium administration and prostate cancer risk was strongest. The difference in biopsy rates could not be accounted for by factors such as PSA concentration, age at which abnormal PSA was detected, or alternative diagnostic procedures. Although a difference this large could have occurred by chance, this finding raises concerns about possible disruption of blinding. Investigators provided no information as to the prostate biopsy rate among participants with lower PSA levels or biopsy rates for the primary outcome of non-melanoma skin cancer, which also requires pathological confirmation, nor for the secondary outcomes examined in this trial.

Observational studies

We presented in Table 2 a summary of study ratings according to the Newcastle-Ottawa Scale (NOS). The median number of assigned stars was eight for both (nested) case-control and cohort study assessments, out of a maximum of nine stars each.

All but one cohort study received five to nine stars on the NOS. The exception (two stars) was an early investigation that was available only in abstract form for assessment (Clark 1985). In the NOS cohort assessment, we considered representativeness of the cohort for the target population to be adequate in 59% of studies, which received a star; 79% of studies provided evidence that

cancer was not present at study commencement; we considered completeness of follow-up (≥ 95%) data to be adequate in 93% of studies. The representativeness of the cohort for the target population is a matter of external validity and generalisability of study results, but a systematic deviation of participants from the target population might also introduce bias into study results. The target population of included studies varied with study objectives and could have been the general population, as well as special occupational groups. We did not assign a star for this question to studies that did not identify their target population or to studies that recruited volunteers. Differential selection of study participants (e.g. volunteers) from the target population can lead to confounding by factors associated with selenium status and cancer incidence (e.g. nutritional behaviour, socioeconomic position). All included studies chose comparison groups (cases/controls or exposed/non-exposed) from the same study population. This approach enhanced comparability between groups.

We considered follow-up data as complete or as missing data unlikely to introduce bias to study results in 47% of included observational studies. In the other cohorts, losses to follow-up were greater than 5% and trial authors did not provide a description of losses to follow-up. A high attrition rate may alter the characteristics of the population under investigation and may impede the generalisability of study results to the intended target population (external validity). The presence of attrition does not necessarily mean that study results are biased. However, given the possibility that selenium status may be linked to sociodemographic variables and socioeconomic position, which may also influence participation in follow-up procedures, a differential effect of attrition may introduce bias towards underestimation or overestimation of the true exposure effect.

Forty-five included observational studies were nested case-control studies; therefore we assessed them by using the NOS case-control form. The number of stars in the NOS assessment of case-control studies ranged from five to nine, with 87% of studies receiving eight or nine stars. Although we generally assessed included prospective case-control studies as having low risk of bias, we had concerns regarding case definition and the question of the representativeness of cases in some studies.

We considered the definition of cases as inadequate in 24% of nested case-control studies, as cases were identified by self-reporting; investigators did not describe linkage to databases with unclear validity or procedures. The magnitude and direction of bias that might have been introduced to the study results remain unclear.

In 16% of studies, investigators did not include all identified cases (or an appropriate sample of them) in the trial analyses, or they did not report selection procedures for analysed cases. Some studies lost blood specimens as the result of technical problems (e.g. cooler breakdown at one study centre); other studies reported that material available for analysis was insufficient; and others selected cases for analysis in a non-random manner. This might bias the estimates of association in either direction.

We noted no obvious asymmetry (as an indicator of publication bias) in the funnel plots of studies on total cancer risk (Figure 3) and selected cancer types (Figure 4; Figure 5; Figure 6).

Figure 3. Funnel plot of comparison: 1 Highest versus lowest selenium exposure, outcome: 2.1 Total cancer incidence and mortality.

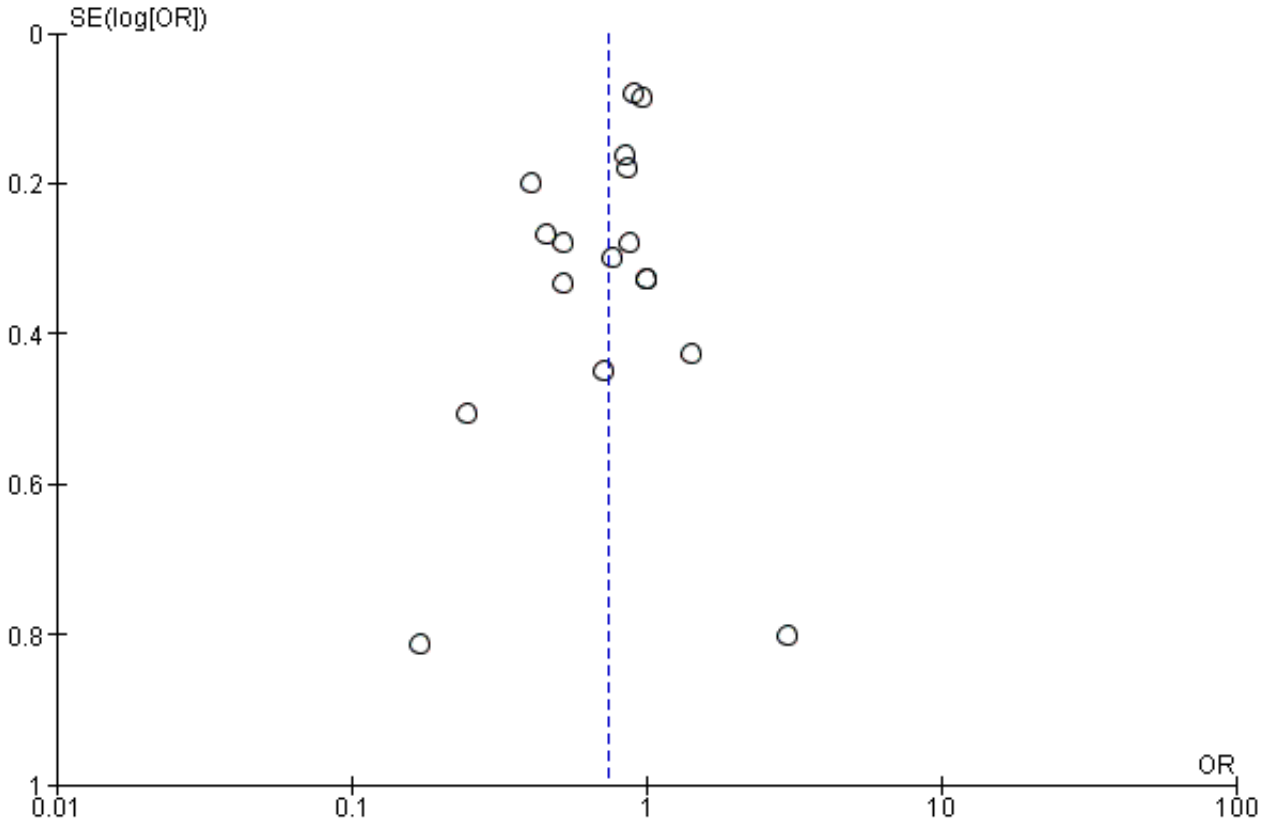


Figure 4. Funnel plot of comparison: 1 Observational studies: highest versus lowest selenium exposure, outcome: 2.8 Colorectal cancer risk.

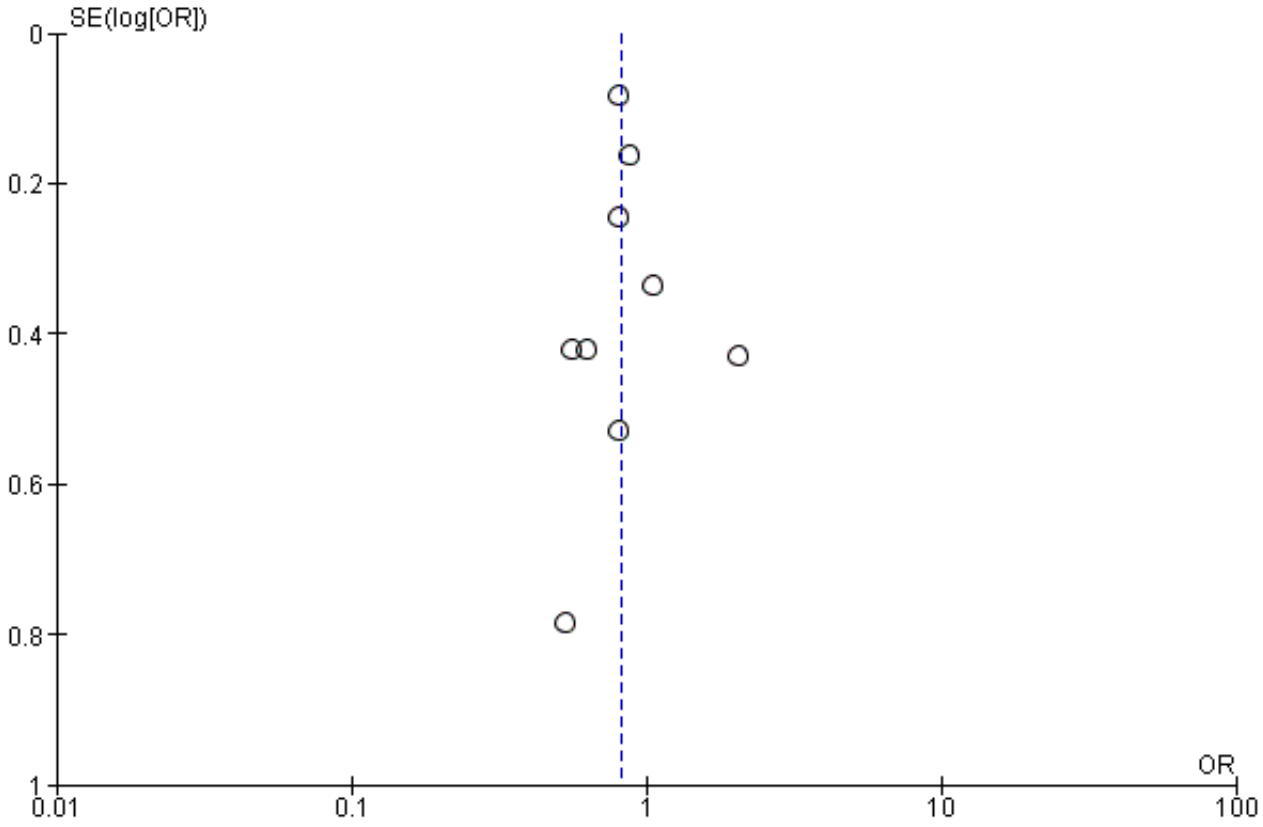


Figure 5. Funnel plot of comparison: 1 Observational studies: highest versus lowest selenium exposure, outcome: 2.12 Lung cancer risk incidence and mortality

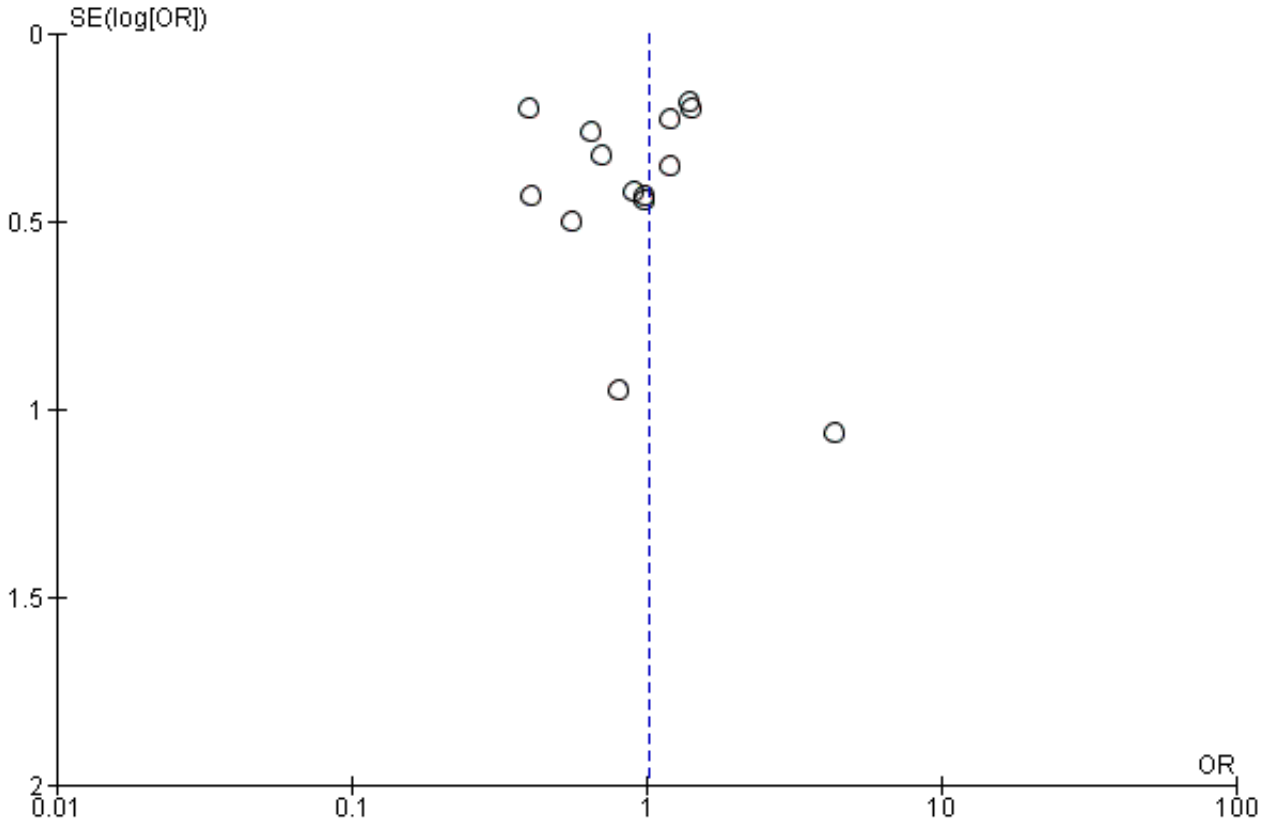
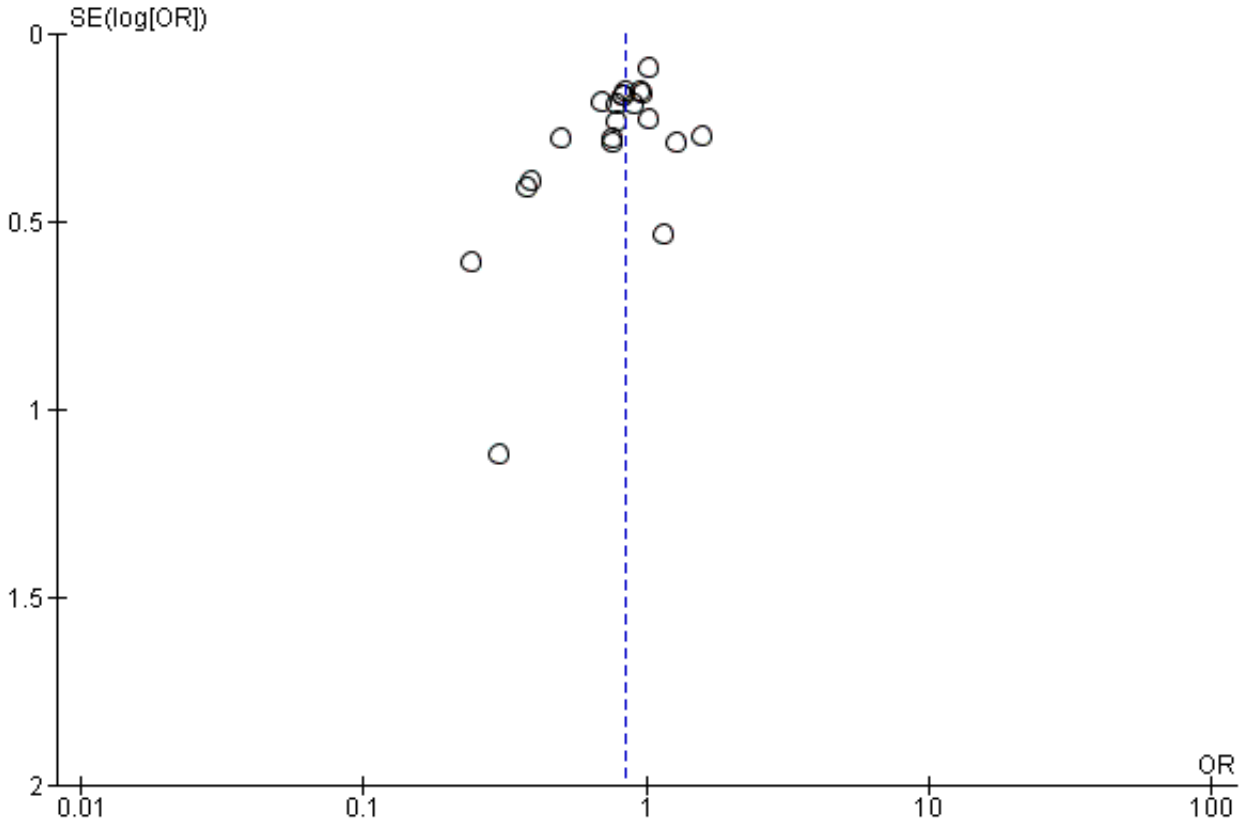


Figure 6. Funnel plot of comparison: 1 Highest versus lowest selenium exposure, outcome: 2.19 Prostate cancer risk.



Ethical criteria

All trials fulfilled informed consent and ethics board approval criteria (Algotar 2013; Dreno 2007; Karp 2013; Marshall 2011; NPCT 2002; Reid 2008; SELECT 2009), except for Li 2000, Yu 1991, Yu 1997, and Lubinski 2011, which did not mention these criteria.

Effects of interventions

See: **Summary of findings for the main comparison** Highest compared with lowest selenium exposure for preventing cancer in randomised controlled studies with low risk of bias; **Summary of findings 2** Highest compared with lowest selenium exposure for preventing cancer in observational studies

1. Randomised controlled trials

We reported results from Duffield-Lillico 2002 for all outcomes evaluated in the NPCT study (NPCT 2002) (prostate cancer, lung cancer, bladder cancer, colorectal and breast cancer, any cancer, and death from cancer), except for prostate cancer, for which we also used Duffield-Lillico 2003a, in: NPCT 2002, and for the primary outcome, non-melanoma skin cancer, whose results were reported in Duffield-Lillico 2003b, in: NPCT 2002. For the SELECT study (SELECT 2009), we included only results from Lippman 2009, in: SELECT 2009, which reported on the blinded period of follow-up with continuing selenium supplementation - not from Klein 2011, in: SELECT 2009, which reported a longer period of follow-up, including a subsequent period without selenium supplementation, and was discontinued in 2008 in compliance with the recommendation of the trial's independent DSMC (Lippman 2009 and Klein 2011, in: SELECT 2009). This second report by Klein et al included an additional period of 32 months (23% person-time increase), along with the first follow-up period, and results were essentially similar to those of Lippman et al 2009. For bladder cancer risk in SELECT, we used data from Lotan 2012, in: SELECT 2009, which encompassed the same extended period of follow-up as Klein 2011, in: SELECT 2009, but was the only report available from the SELECT trial on this cancer type. For prostate cancer in SELECT, we also evaluated three reports published in 2014 that addressed specific population subgroups and cancer subtypes (Albanes 2014; Kristal 2014; Martinez 2014). For the ECOG trial, we used the 2013 report for all cancer types (Karp 2013).

1.1. Preventive efficacy outcomes

1.1.1. Any cancer incidence and mortality

Five studies evaluated the outcome of any cancer incidence (Algotar 2013; Karp 2013; Lubinski 2011; NPCT 2002; SELECT 2009); we assessed three of these trials as having low risk of bias (Algotar 2013; Karp 2013; SELECT 2009). Risk ratios (RRs) were based on detection of 1043 cases among 10,026 participants receiving supplemental selenium and 942 cases among 9449 participants allocated to placebo. We found no evidence of reduced incident cancer risk in studies at low risk of bias (RR 1.01, 95% confidence interval (CI) 0.93 to 1.10), nor in the analysis including all studies (RR 0.99, 95% CI 0.86 to 1.14) (Analysis 1.1).

When we evaluated mortality from all cancers as an outcome, we could include only two studies in the analysis (NPCT 2002; SELECT 2009), one of which was at low risk of bias (SELECT 2009). When we considered only this latter trial, no difference in mortality rates between selenium and placebo arms emerged (RR 1.02, 95% CI 0.80 to 1.30). However, when we considered all studies, risk in the selenium group was lower than risk in the placebo group (RR 0.81, 95% CI 0.49 to 1.32) (Analysis 1.2).

1.1.2. Head and neck cancer

Two trials investigated effects of selenium supplementation on risk of head and neck cancer (Karp 2013; NPCT 2002), but only one was at low risk of bias (Karp 2013). In analysis restricted to the study having low risk of bias, no relation emerged for the risk of this cancer type, with a summary RR of 1.00 (95% CI 0.18 to 5.45), and analysis pooling both studies yielded statistically unstable risk estimates (RR 1.22, 95% CI 0.52 to 2.85), based on 13 cases in the selenium arms and 9 cases in the placebo arms (Analysis 1.3).

1.1.3. Esophageal cancer

Two RCTs investigated the risk of oesophageal cancer associated with selenium supplementation (Karp 2013; NPCT 2002), but only one was at low risk of bias (Karp 2013). The number of cases in these studies was very low (3 in the selenium arms and 5 in the placebo arms), thus yielding very imprecise RR estimates. The summary RR for oesophageal cancer was 1.50 (95% 0.06 to 36.86) in the only study with low risk of bias, and 0.53 (95% CI 0.12 to 2.28) in overall studies (Analysis 1.4).

1.1.4. Colorectal cancer

Three randomised controlled trials investigated the risk of colorectal cancer following selenium supplementation. These studies reported 76 cases in the selenium arms and 83 cases in the placebo arms (Karp 2013; NPCT 2002; SELECT 2009); two were at low risk of bias (Karp 2013; SELECT 2009). The summary RR of colorectal cancer was 0.99 (95% CI 0.69 to 1.43) in the two studies with low risk of bias, and 0.74 (95% CI 0.41 to 1.33) in all studies (Analysis 1.5).

1.1.5. Liver cancer

Four RCTs investigated the efficacy of selenium supplementation for liver cancer prevention, three of which were conducted in China with participants of different high-risk groups in Qidong province, and one in the United States among individuals with resected non-small-cell lung cancer (Karp 2013; Li 2000; Yu 1991; Yu 1997). Yu 1991 reported on a trial with 2474 male and female first-degree relatives of patients with liver cancer. During the study period of two years, investigators observed 10 participants in the selenium group, who received 200 µg selenium yeast/d, and 13 cases in the placebo group (RR 0.55, 95% CI 0.24 to 1.25). Yu 1997 investigated a four-year supplementation period with 200 µg selenium yeast/d in 226 male and female hepatitis B-surface antigen (HBs-Ag) carriers. Investigators detected 11 cases (person-time incidence rate: 1573.03/100,000) in the placebo group and four cases in the selenium group (RR 0.36, 95% CI 0.12 to 1.11) during the eight-year follow-up period. The mean blood selenium level during the intervention period was 152 µg/L in the intervention group and 107 µg/L in the control group. Li 2000 randomly assigned 2065 male HBs-Ag carriers to receive 0.5 mg sodium selenite or placebo daily for three years. Thirty-four cases of liver cancer occurred among 1112 participants receiving selenium, and 57 cases occurred among 953 placebo participants (RR 0.51, 95% CI 0.34 to 0.77).

Karp 2013 allocated 521 individuals with history of resected non-small-cell lung cancer to 200 µg/d selenium as selenised yeast or to placebo. During follow-up, investigators diagnosed six new cases of liver cancer (actually coded as occurring to the 'liver, gallbladder and bile duct')- all in the selenium arm. We deemed this study to have low risk of bias.

The three Chinese studies had unclear risk of bias owing to lack of clear reporting of generation of allocation sequence or allocation concealment, and/or completeness of outcome data. Limiting analysis to the only study not downgraded owing to risk of bias yielded an RR of 6.52 (95% CI 0.37 to 115.49) (Analysis 1.6). The overall RR of the four studies was 0.52 (95% CI 0.35 to 0.79).

1.1.6. Melanoma

Three RCTs investigated the risk of melanoma following selenium supplementation (Algotar 2013; Karp 2013; NPCT 2002), but we judged only two of them to have low risk of bias (Algotar 2013; Karp 2013). For eight cases in the selenium arms and four cases in the placebo arms, the summary RR estimate was 1.35 (95% CI 0.41 to 4.52) in RCTs at low risk of bias. The RR estimate was slightly lower when all studies were considered (RR 1.28, 95% CI 0.63 to 2.59) (Analysis 1.7).

1.1.7. Non-melanoma skin cancer

1.1.7.1. Total non-melanoma skin cancer

Risk of non-melanoma skin cancer was the primary outcome of the NPCT,which reported higher risk in the selenium-supplemented group than in the placebo group (unadjusted RR 1.27, 95% CI 1.11 to 1.45) (Duffield-Lillico 2003a, in: NPCT 2002). This increase was confirmed by multi-variable analysis after adjustment for confounders (hazard ratio (HR) 1.17, 95% CI 1.02 to 1.34) and was concentrated among participants in the highest two tertiles of baseline plasma selenium (≥ 105.6 µg/L), although increased risk for total non-melanoma skin cancer was seen in all tertiles of baseline plasma selenium levels (Reid 2008). No variation in this effect appeared to be induced by age, sex, or smoking habits, and eliminating cases that occurred during the first period of selenium supplementation (one to two years) induced a slight decline in RRs. The mean selenium plasma concentration for participants was 114 µg/L at the time of randomisation. In the arm of the NPCT that was carried out in a single location - Macon, Georgia, USA - and included both 200 and 400 µg/d selenium supplementation (Reid 2008), non-melanoma skin cancer risk increased in the 200-µg/d arm after adjustment for age, sex, and smoking (unadjusted RR 1.49, 95% CI 1.10 to 2.03; adjusted HR 1.50, 95% CI 1.13 to 2.04) but not in the 400-µg/d arm (unadjusted RR 0.88, 95% CI 0.66 to 1.16; adjusted HR 0.91, 95% CI 0.69 to 1.20). At the remaining sites, where only 200 µg/d of supplemental selenium was given, the RR was 1.24 (95% CI 1.07 to 1.45) and the HR was 1.18 (95% CI 1.02 to 1.37). Distribution of baseline plasma selenium levels was similar in this substudy to that in the NPCT main study, and no evidence of effect modification according to baseline selenium exposure emerged. Overall, the NPCT did not support preventive efficacy of selenium yeast supplementation against non-melanoma skin cancer in these populations; on the contrary, investigators reported a cancer-promoting effect of selenium for this cancer type, which

was the primary trial endpoint, raising concern about potentially harmful effects of such selenium supplementation (NPCT 2002).

SELECT, which is the largest selenium supplementation trial conducted to date (Lippman 2009 and Klein 2011, in: SELECT 2009), thus far has not investigated the incidence of non-melanoma skin cancer. A small trial in a French population of 184 organ graft recipients who were considered to be at high risk of premalignant and malignant epithelial lesions (Dreno 2007) investigated non-melanoma skin cancer. This trial detected a higher incidence of skin cancer among 91 selenium-supplemented participants (six cases; 6.6%) compared with 93 placebo-supplemented participants (two cases; 2.2%; P = 0.15) during a five-year follow-up, which in its first three years comprised daily supplementation with selenised yeast containing 200 µg selenium.

A small trial among participants at high risk for prostate cancer also investigated the effects of using selenium supplements of 200 and 400 µg/d on risk of non-melanoma skin cancer, with a median follow-up of three years (Algotar 2013). Results for non-melanoma skin cancer from this study showed the occurrence of three cases among 232 placebo-treated participants and 11 cases among 467 selenium-supplemented participants (eight cases among 234 individuals receiving 200 µg/d of selenium, and three cases among 233 individuals receiving 400 µg/d), with increased risk after overall selenium supplementation (incidence rate ratio from our calculation 1.8, 95% CI 0.5 to 10.2) but no evidence of a dose-response relation.

The ECOG trial investigated non-melanoma skin cancer and found 19 cases during follow-up of 521 placebo-treated participants and 11 cases among 1040 selenium-allocated participants (Karp 2013). The RR of non-melanoma skin cancer in this study was computed as 0.66(95% CI 0.37 to 1.19).

Overall, the summary RR for non-melanoma skin cancer in selenium-supplemented participants could be computed by pooling RRs from the above trials, rather than by using numbers of participants and cases, because the number of skin cancer cases diagnosed in the NPCT was not reported in the relevant publication (Duffield-Lillico 2003a, in: NPCT 2002). The estimated RR limited to the only two trials with low risk of bias indicated a statistically unstable increased risk of non-melanoma skin cancer associated with selenium supplementation of 200 µg/d (RR 1.16, 95% CI 0.30 to 4.42), with similar risk results when analysis was performed on the four trials overall (RR 1.23, 95% CI 0.73 to 2.08) (Analysis 1.8) (Algotar 2013; Karp 2013).

1.1.7.2. Basal cell carcinoma (BCC)

Algotar 2013 found in the 200- and 400-µg/d selenium groups an RR of 0.86 (95% CI 0.42 to 1.77) and 0.80 (95% CI 0.38 to 1.66), respectively; and an RR in both treatment groups combined of 0.83 (95% CI 0.45 to 1.54). ECOG 5597 found an RR of 0.54 (95% CI 0.26 to 1.14) (Karp 2013).

At the end of the blinded treatment period in NPCT 2002, the unadjusted RR for basal cell carcinoma in the 200-µg/d selenium group was 1.17 (95% CI 1.02 to 1.35), and the adjusted HR was 1.09 (95% CI 0.94 to 1.26). Eliminating cases that occurred within the first two years of supplementation had no effect on the RR. Reid 2008 found a crude RR of 0.90 (95% CI 0.65 to 1.24) and an adjusted HR of 0.95 (95% CI 0.69 to 1.29) for this cancer type in the 400-µg/d selenium substudy. In a small trial with no RR estimates (Dreno 2007), three cases of BCC occurred among 91 selenium-supplemented participants, along with one case among 93 placebo-receiving participants.

1.1.7.3. Squamous cell carcinoma (SCC)

Algotar 2013 found an RR of 0.58 (95% CI 0.27 to 1.25) and 0.12 (95% CI 0.03 to 0.50) in the 200- and 400-µg/d trial populations, respectively, and for all participants, the RR was 0.35 (95% CI 0.17 to 0.72). ECOG 5597 found an RR of 0.92 (95% CI 0.34 to 2.47) (Karp 2013).

In NPCT 2002, selenium supplementation increased the risk of SCC (unadjusted RR 1.32, 95% CI 1.09 to 1.60; adjusted HR 1.25, 95% CI 1.03 to 1.51). Adverse effects of selenium supplementation on SCC risk appeared to increase with increasing plasma selenium levels at baseline, in that higher risk was seen only in participants at the highest two tertiles of baseline levels (≥ 105.6 µg/L), suggesting an interaction between supplementation and baseline exposure. In the 400-µg/d selenium substudy (Reid 2008), investigators reported no change in SCC risk by selenium supplementation (crude RR 1.20, 95% CI 0.85 to 1.68; adjusted HR 1.05, 95% CI 0.71 to 1.56). Dreno 2007, the smaller trial, reported that two among 91 selenium-supplemented individuals were given a diagnosis of SCC, whereas no cases were observed among placebo participants.

1.1.8. Lung cancer

Three RCTs have investigated lung cancer risk associated with selenium administration (Karp 2013; NPCT 2002; SELECT 2009), with two assessed as having low risk of bias (Karp 2013; SELECT 2009). Summary RR estimates were 1.16 (95% CI 0.89 to 1.50) when we limited the analysis to studies at low risk of bias, and 1.03 (95% CI 0.78 to 1.37) when we included all studies (Analysis 1.9).

1.1.9. Female breast cancer

Three studies evaluated breast cancer risk associated with selenium supplementation (Karp 2013; Lubinski 2011; NPCT 2002), one of which we judged as having low risk of bias (Karp 2013). The RR from the study with low risk of bias was 2.04 (95% CI 0.44 to 9.55), with statistical imprecision due to the small number of cases (eight in the selenium arm, two in the placebo arm). The pooled RR from all studies was 1.44 (95% CI 0.96 to 2.17) (Analysis 1.10).

1.1.10. Bladder cancer

Three studies evaluated bladder cancer outcomes (Karp 2013; NPCT 2002; SELECT 2009), two of which we judged as having low risk of bias (Karp 2013; SELECT 2009), The summary RR from the only studies at low risk of bias was 1.07 (95% CI 0.76 to 1.52). The corresponding RR for all studies, encompassing a total of 146 cases - 79 in the selenium arms and 67 in the placebo arms - was 1.10 (95% CI 0.79 to 1.52) (Analysis 1.11).

1.1.11. Prostate cancer

Five trials evaluated prostate cancer (Algotar 2013; Karp 2013; Marshall 2011; NPCT 2002; SELECT 2009), all of which we judged as having low risk of bias, except for NPCT 2002. Meta-analysis for prostate cancer-based trials at low risk of bias yielded an RR of 1.01 (95% CI 0.90 to 1.14) for the 9630 participants supplemented with selenium (520 cases) compared with the 9312 participants allocated to placebo (500 cases), indicating no effect of intervention (supplementation of organic selenium at 200 µg/d) on prostate cancer risk, with very consistent results and no heterogeneity

across these studies (I^2 = 0.0%). The overall RR was 0.91 (95% CI 0.75 to 1.12) when all studies were considered; moderate heterogeneity (I^2 = 36%) emerged owing to the addition of the NPCT (Analysis 1.12) (NPCT 2002).

The trial that first investigated the relation between selenium exposure and prostate cancer risk (Duffield-Lillico 2002 and Duffield-Lillico 2003b, in: NPCT 2002) reported a reduction in prostate cancer incidence in the selenium-treated group, which was particularly strong during the first period of follow-up (1983 to 1993; adjusted HR 0.35, 95% CI 0.16 to 0.65) and was slightly higher but still much lower than unity during the entire period of follow-up (1983 to 1996; HR 0.48, 95% CI 0.28 to 0.80). Analyses stratified by baseline plasma selenium category showed greatly reduced risk associated with active treatment among participants with baseline plasma selenium ≤ 106.4 µg/L (HR 0.14, 95% CI 0.03 to 0.61) in the intermediate category (106.8 to 123.2 µg/L; HR 0.33, 95% CI 0.13 to 0.82), while in the upper category (> 123.2 µg/L), the HR was 1.14 (95% CI 0.51 to 2.59). Selenium supplementation in participants with baseline PSA ≤ 4 ng/mL was associated with considerably reduced risk (HR 0.33, 95% CI 0.14 to 0.79) compared with risk in individuals with PSA > 4 ng/mL (HR 0.95, 95% CI 0.42 to 2.14). However, interpretation of these NPCT findings is complicated by a potentially serious source of bias. As reported in 2003 by the study authors, a considerably higher percentage of participants with elevated PSA levels in the placebo group underwent prostatic biopsy as compared with participants in the selenium group (35% vs 14%; P < 0.05; Duffield-Lillico 2003b, in: NPCT 2002). Differences in biopsy rates were greatest among participants with the lowest baseline selenium concentrations - the subgroup that appeared to derive the greatest beneficial effects of selenium administration. This may have contributed to substantial overestimation of the effects of selenium supplementation in the NPCT.

The SELECT trial found no evidence of benefit derived from selenium supplementation (compared with placebo) over a median of 5.5 years in terms of prostate cancer incidence (HR 1.03, 95% CI 0.90 to 1.18, 99% CI 0.87 to 1.24) (SELECT 2009). The adjusted HR for prostate cancer in the selenium plus vitamin E group compared with the placebo group was 1.05 (95% CI 0.91 to 1.20, 99% CI 0.88 to 1.25). The original report of the trial provided no specific RR estimate according to disease severity, but during an extended follow-up of this cohort after selenium supplementation had ceased (Klein 2011, in: SELECT 2009), investigators found increased risk of Gleason 7 or greater disease (HR 1.21, 99% CI 0.90 to 1.63). It is interesting to note that the SELECT trial included only participants with PSA ≤ 4 ng/mL - the group in the NPCT that showed greatest apparent benefit. During this further follow-up of the SELECT cohort, risk of prostate cancer in the selenium arm also slightly increased compared with that described in the first report, which had included only the active supplementation period (Lippman 2009, in: SELECT 2009). In this longer follow-up based on 575 prostate cancer cases in the selenium arm and 529 in the placebo arm, the RR of prostate cancer was 1.09 (99% CI 0.93 to 1.27).

Three further reports from SELECT on the relation between selenium administration and prostate cancer risk have been published (Albanes 2014; Kristal 2014; Martinez 2014); where investigators looked at more specific associations than were addressed in the two main publications from this trial (Lippman 2009 and Klein 2011, in: SELECT 2009). Kristal 2014 performed a case-cohort study within the SELECT study by including 1739 total prostate cancer cases (of which 489 showed high-grade (Gleason 7 to 10) disease) and 3117 randomly selected men composing the control subcohort (Kristal 2014). Administration of selenium (both selenium only and selenium combined with vitamin E) had no effect on prostate cancer risk among men with low baseline selenium status (< 60th percentile of toenail selenium), but among participants in the two upper quintiles of baseline selenium exposure, risk of prostate cancer was increased (HR 1.20, 95% CI 0.85 to 1.81), particularly high-grade prostate cancer (HR 1.62, 95% CI 0.95 to 2.77). HRs were even higher when any selenium supplementation (alone or with vitamin E) was considered because such supplementation increased the risk of any prostate cancer (RR 1.27, 95% CI 0.92 to 1.74) and high-grade disease (RR 1.91, 95% CI 1.20 to 3.05).

Martinez 2014 investigated the effect of selenium supplementation on prostate cancer risk among participants in SELECT who had genotypes associated with altered mRNA expression of the androgen-regulated prostate tumour suppressor protein NKX3.1. The design was still of the case-cohort type, encompassing 1866 prostate cancer cases and 3135 non-prostate cancer cases. Trial authors found that selenium administration combined with the CC genotype at rs11781886 increased overall prostate cancer risk (HR 1.68, 95% CI 1.01 to 2.78) and low-grade prostate cancer risk (HR 1.81, 95% CI 1.02 to 3.23), but they noted no such interaction for the other genotypes.

Finally, in a SELECT subpopulation composed of 1746 prostate cancer cases and a subcohort of 3211 men, Albanes 2014 investigated a possible association between baseline plasma α-tocopherol and γ-tocopherol and active supplementation with selenium (and vitamin E as α-tocopherol) in terms of prostate cancer risk. Trial authors found a strong excess of risk among participants in the highest baseline α-tocopherol category (fifth quintile) receiving selenium supplementation (HR 2.04, 95% CI, 1.29 to 3.22, P trend 0.005), which was higher with high-grade (Gleason grade 7 to 10) disease among men receiving selenium (HR 2.12, 95% CI, 1.32 to 3.40, P-trend 0.0002). These findings suggest a possible biological interaction between α-tocopherol status and selenium supplementation in increasing high-grade prostate cancer risk.

In Marshall 2011, prostate cancer incidence was 35.6% versus 36.6% in selenium-supplemented compared with placebo-treated participants after three years of follow-up, respectively. The overall RR was 0.91, with a 95% CI of 0.55 to 1.52 (courtesy of James Marshall, unpublished data). Analysis of RRs according to baseline plasma selenium levels showed no dose-response effect, with point estimates of 0.82 (95% CI 0.40 to 1.69), 1.38 (95% CI 0.68 to 2.78), 0.98 (95% CI 0.58 to 1.68), and 0.91 (95% CI 0.45 to 1.84), when the quartile of selenium status was increased at baseline.

The NBT reported an HR of prostate cancer of 0.94 (95% CI 0.52 to 1.70) for participants receiving 200 µg/d and 0.90 (95% CI 0.48 to 1.66) for those receiving 400 µg/d, compared with placebo (Algotar 2013). Although average baseline selenium status, as assessed through plasma selenium, was higher than in the NPCT (median value 126.1 vs 115.0 µg/L), the lowest tertile of plasma selenium levels had a median value (101.1 µg/L) well below the apparent threshold of around 120 µg/L, at which a beneficial effect of selenium seemed to occur in the NPCT. Furthermore, as noted by study authors, 45% of participants enrolled in this study had baseline plasma selenium levels < 123 µg/L, which is the upper

threshold for a protective effect of selenium supplementation according to results of the NPCT. Trial authors also stated: "None of the baseline variables modified the effect of selenium on the primary endpoint", and plasma selenium concentration at baseline was among these variables (Algotar 2013).

Karp 2013, the ECOG trial, carried out in subjects with resected non-small-cell lung cancer, reported nine and 16 cases of newly diagnosed prostate cancer among 250 and 509 male participants in the placebo and selenium groups, respectively. This allowed us to compute an RR of 0.87 (95% CI 0.39 to 1.45) for prostate cancer in the selenium-supplemented arm.

Following the NPCT, none of the subsequent, high-quality RCTs provided evidence suggesting that baseline selenium status could modify the effect of selenium supplementation on subsequent prostate cancer occurrence. In the NBT, the bottom category (tertile) of baseline plasma selenium levels in this trial population was 101.1 µg/L, i.e. lower than the upper bound of the bottom category (106.4 µg/L) and the middle category (106.8 to 123.2 µg/L) in the NPCT, both of which had shown a strongly decreased subsequent prostate cancer occurrence (Algotar 2013). In the SWOG S9917 study, results of selenium supplementation were also made available for four categories (quartiles) of baseline plasma selenium and showed no effect of treatment in any categories (Marshall 2011). These categories were < 106, 106–132, 132–162, and > 162 µg/L, and corresponding RRs of prostate cancer in the selenium-supplemented group were 0.82 (95% CI 0.40 to 1.69), 1.38 (95% CI 0.68 to 2.78), 0.98 (95% CI 0.58 to 1.68), and 0.91 (95% CI 0.45 to 1.84), respectively, versus an overall study RR of 0.97 (95% CI 0.68 to 1.39). Therefore, also in this high-quality trial, the bottom category of baseline selenium exposure was entirely similar to the corresponding one in the NPCT, but in contrast to NPCT, no effect of selenium supplementation emerged and no evidence showed risk of bias. Finally, a case-cohort study carried out within SELECT and published in 2014 provided data showing the relation between baseline selenium exposure and effects of selenium supplementation (Kristal 2014). In that study, whose average selenium exposure was higher than that characterising the NPCT and the NBT, investigators reported no effect of selenium supplementation on both overall prostate cancer and low-grade and high-grade prostate cancer in the three quintiles of baseline toenail selenium levels, but enhanced risk of high-grade prostate cancer emerged for the two upper quintiles (alone and combined). Quintile cutoff points for these categories of the trial population were 0.758, 0.832, 0.901, and 1.003 µg/g. Overall, these results clearly indicate that even in subgroups with the lowest baseline selenium status in these Western populations, selenium provided no protective effect for prevention of prostate cancer, although this is the cancer type that once was thought to be most strongly associated with a beneficial effect of selenium supplementation.

1.1.12. Haematological cancers

Two trials evaluated the risk of haematological malignancies associated with selenium administration (Karp 2013; NPCT 2002) using 23 cases only - 14 in the selenium arms and 9 in the placebo arms - but we judged only one trial to be at low risk of bias (Karp 2013). The summary RR was 1.00 (95% CI 0.25 to 3.99) in the study at low risk of bias and 1.21 (95% CI 0.52 to 2.80) when all studies were considered (Analysis 1.13).

1.2. Adverse effects outcomes

The RCTs on selenium have provided unexpected information about the incidence of adverse effects of selenium supplementation and have unexpectedly become a key source of data for risk assessment of the upper safe level of selenium exposure in humans (Vinceti 2017a; Vinceti 2017b). Thirty-five participants withdrew from the NPCT because of adverse effects, mainly gastrointestinal upset. The RR for adverse events in the selenium group was 1.51 (95% CI 0.74 to 3.11) (our calculation, based on the number of randomly assigned participants). Reports of increased risk of glaucoma in Marshall 2011 and NPCT 2002 prompted additional studies on this issue (Bruhn 2009), and likely led to inclusion of cataract and glaucoma among the several potential adverse events monitored during subsequent trials in which investigators administered selenium (Algotar 2013).

In the NPCT, a secondary analysis of participants who did not have diabetes at the start of the study unexpectedly revealed an excess risk of type 2 diabetes mellitus in the selenium group (adjusted HR 1.55, 95% CI 1.03 to 2.33) (Stranges 2007). That study found increased risk of developing type 2 diabetes associated with selenium supplementation across all tertiles of baseline plasma selenium levels, although the excess was much greater for the upper category of > 121.6 µg/L (RR 2.70, 95% CI 1.30 to 5.61) than for the lower (RR 1.13, 95% CI 0.58 to 2.18) and intermediate (RR 1.36, 95% CI 0.60 to 3.09) categories. Increased risk of diabetes associated with selenium supplementation was independent of baseline age, sex, smoking status, and body mass index (BMI), with the exception of participants in the top tertile of BMI. SELECT reported a slight increase in the incidence of type 2 diabetes in the selenium-alone group (RR 1.07, 99% CI 0.94 to 1.22). Any such excess risk decreased over time after selenium supplementation ceased, as is shown by results of the Klein study (Klein 2011, in: SELECT 2009). In this study, the RR of diabetes was 1.04 (99% CI 0.93 to 1.17), thus supporting a short-term effect of selenium supplementation on diabetes risk.

Although the three trials on liver cancer and Reid 2008 did not mention the occurrence of adverse effects, and Dreno 2007 and Marshall 2011 (the SWOG 2011 trial) apparently performed no assessment of diabetes incidence, three recent phase 3 RCTs have investigated the occurrence of diabetes after selenium supplementation for prevention of malignant and non-malignant cancer. In the NBT, during five years of follow-up of 699 participants at high risk for prostate cancer supplemented with 200 or 400 µg/d of selenium or placebo, Algotar 2013 reported the occurrence of diabetes in 12, 12, and 7 participants, respectively. This allowed us to compute an incidence rate ratio of 1.70 (95% CI 0.62 to 5.10) and 1.71 (95% CI 0.62 to 5.12) among 200- and 400-µg/d selenium-supplemented participants, respectively, compared with those given placebo. The ECOG trial, which was carried out in 1561 participants with resected stage I non–small-cell lung cancer, trial authors did not explicitly report the RR of diabetes during follow-up (Karp 2013). However, occurrence during four years of follow-up (2007 to 2011) was stated as 26 new diagnoses of diabetes in the selenium arm (1040 participants at baseline, of whom 865 underwent toxicity assessment) and 12 new diagnoses among placebo-treated participants (521/477). On the basis of these numbers, we could compute an RR of 1.09 (95% CI 0.55 to 2.13) or, for participants with toxicity assessment, 1.19 (95% CI 0.61 to 2.35) - values comparable with those observed in the other trials, except for NPCT. Most recently, in an intervention study investigating the

effect of selenium supplementation for prevention of colorectal adenoma recurrence compared with placebo (the SELCEL trial), 31 cases of diabetes occurred in the selenium-treated group and 25 in the placebo group during follow-up, with an RR of 1.25 (95% CI 0.74 to 2.11) (Thompson 2016). Therefore, an excess incidence of type 2 diabetes systematically emerged in all trials that investigated this adverse effect (Vinceti 2017b).

The SELECT study also looked at other side effects known to be associated with selenium overexposure (Vinceti 2001), finding an association for some of them. Selenium treatment increased the occurrence of alopecia (RR 1.28, 95% CI 1.07 to 1.53, based on 265/206 cases in selenium and placebo arms), dermatitis (RR 1.16, 95% CI 1.03 to 1.29, 619/524), nail changes (RR 1.04, 95% CI 0.96 to 1.13, 1087/1035), and halitosis (RR 1.17, 95% CI 0.99 to 1.38, 503/427).

2. Observational studies

When risks of cancer for higher and lower levels of selenium exposure are compared, a summary risk estimate of one suggests no association between selenium exposure and cancer, and summary risk estimates below and above one suggest a beneficial or harmful effect of higher selenium exposure, respectively. We evaluated the statistical precision of the point estimates by assessing the width of their 95% or 99% confidence intervals.

2.1. Aetiological association: results from meta-analyses

2.1.1. Any cancer

We meta-analysed results of 16 prospective observational studies on total cancer risk, including data on more than 276,000 participants. The cohorts of Salonen 1984 and Salonen 1985 overlapped. Hence, we included only data from Salonen 1985 in the meta-analysis. We had to omit Fex 1987, as the CI value was not reported and could not be calculated from available data.

For participants in the highest category of pre diagnostic selenium exposure, the summary risk estimate was odds ratio (OR) 0.72 (95% CI 0.55 to 0.93) for cancer incidence and OR 0.76 (95% CI 0.59 to 0.97) for cancer mortality for both sexes combined (Analysis 2.1), when compared with participants in the lowest exposure category. We observed moderate to substantial heterogeneity for both incidence (I^2 = 45%) and mortality (I^2 = 67%).

Analyses by sex revealed lower point estimates for men (incidence: OR 0.72, 95% CI 0.46 to 1.14; mortality: OR 0.65, 95% CI 0.45 to 0.94) (Analysis 2.2) than for women (incidence: OR 0.90, 95% CI 0.45 to 1.77; mortality: OR 0.91, 95% CI 0.80 to 1.03) (Analysis 2.3).

All studies but one (Sun 2016) used a circulating biomarker (serum and plasma selenium levels) for assessment of selenium status. Analysis 2.4 shows the results in ascending order of baseline exposure for those studies that reported category borders. The graph does not reveal any systematic pattern of changes in the relation between selenium status and cancer risk according to increasing baseline selenium levels. Analysis 2.5 shows the results in ascending order for differences in selenium levels.

2.1.2. Stomach cancer

No additional cohort studies on stomach cancer and selenium exposure have been published since the last update of this review; therefore meta-analysis for this cancer type was still based on five studies. The summary risk estimate for both sexes combined was OR 0.66 (95% CI 0.43 to 1.01) in the highest exposure category when compared with the lowest (I^2 = 51%) (Analysis 2.6). In this meta-analysis, we included one cohort twice because trial authors reported results stratified according to cardia and non-cardia gastric cancer (Mark 2000, in: Wei 2004).

Use of available sex-stratified results for meta-analysis yielded a risk estimate for men of OR 0.43 (95% CI 0.14 to 1.32) (I^2 = 56%), and for women of OR 0.73 (95% CI 0.12 to 4.35) (I^2 = 62%) (Analysis 2.7).

2.1.3. Colorectal/Colon cancer

Six observational studies reported data on the incidence of colorectal cancer. The summary risk estimate was OR 0.82 (95% CI 0.72 to 0.94) for both sexes combined (I^2 = 0.0%) (Analysis 2.8), with OR 0.86 (95% CI 0.65 to 1.16) for men and OR 0.96 (95% CI 0.61 to 1.50) for women (Analysis 2.9). Five studies reported data stratified or restricted to colon cancer. The summary estimate was OR 0.81 (95% CI 0.69 to 0.96) for both sexes combined (I^2 = 0.0%) (Analysis 2.10), with OR 0.84 (95% CI 0.56 to 1.25) for men and OR 0.68 (95% CI 0.44 to 1.04) for women (Analysis 2.11).

2.1.4. Lung cancer

We included 13 studies in this meta-analysis. We did not meta-analyse data from Menkes 1986 and Knekt 1990, as the study population of the former overlapped with that of Comstock 1997 (another meta-analysed study) - and results of the latter were presented in insufficient detail.

The summary risk estimate for lung cancer incidence for both sexes combined was 0.82 (95% CI 0.59 to 1.14) (Analysis 2.12). We noted substantial heterogeneity among study results (I^2 = 66%). We found little difference in summary estimates when results were disaggregated by sex (Analysis 2.13), by indicator of selenium exposure (intake, blood or toenail content) (Analysis 2.14), by baseline serum/plasma bottom exposure category (Analysis 2.15), and by ascending differences in selenium levels (Analysis 2.16). In the latter analyses, we noted no dose-response relation between baseline selenium and risk.

2.1.5. Female breast cancer

We included eight studies in this meta-analysis. Data show little association between baseline selenium levels and breast cancer risk, with a slightly but imprecisely higher risk for higher exposure (OR 1.09, 95% CI 0.87 to 1.37) (Analysis 2.17). The heterogeneity of results was low (I^2 = 14%).

2.1.6. Bladder cancer

Meta-analysis of bladder cancer incidence in five observational studies revealed an inverse association, with an overall risk estimate of 0.67 (95% CI 0.46 to 0.97) (Analysis 2.18) (heterogeneity: I^2 = 30%). Sex-disaggregated data were available only from Michaud 2005 and showed an inverse association between selenium exposure and risk in women, but not in men. Two studies included only male participants (Michaud 2002; Nomura 1987); both found a reduced but imprecisely estimated bladder cancer risk for higher selenium exposure (Analysis 2.18). Heterogeneity was not reduced by sex stratification (I^2 = 40% in study results for men). No further studies had been published since the last update of this review (Vinceti 2014).

2.1.7. Prostate cancer

We included 21 epidemiological studies on prostate cancer incidence in the meta-analysis. The summary risk estimate for higher selenium exposure was OR 0.84 (95% CI 0.75 to 0.95) (heterogeneity: I^2 = 27%) (Analysis 2.19). Stratification of the analysis by method of selenium assessment revealed an inverse association between baseline selenium and risk when exposure was assessed through blood selenium levels (OR 0.86, 95% CI 0.75 to 0.99) or toenails (OR 0.60, 95% CI 0.44 to 0.82), but not when dietary assessment methods were used (OR 0.99, 95% CI 0.85 to 1.15) (Analysis 2.20). When we stratified analysis according to baseline (blood) selenium exposure or differences in selenium (blood) levels, no specific relation or pattern emerged between selenium and prostate cancer risk across the entire exposure spectrum (Analysis 2.21; Analysis 2.22).

2.2. Aetiological association: other results

For all other types of cancer, data were available from fewer than five epidemiological studies; thus we did not meta-analyse the results. We have reported in Table 3 results of observational studies not included in meta-analyses. None of these study results support an association between selenium exposure and gynaecological cancer risk, and results for cancers of the gastrointestinal, respiratory, or urological tract are inconsistent. For respiratory and urological cancers, studies reported either no association or increased risk for participants with higher selenium exposure. For gastrointestinal cancers including cancer of the liver and other sites not mentioned above, studies found either no association or reduced risk with higher selenium exposure.

DISCUSSION

Summary of main results

The aims of this review were to examine the efficacy of selenium supplementation in preventing cancer and, more generally, to analyse the association between selenium exposure and risk of cancer in men and women.

Randomised controlled trials (RCTs) and preventive efficacy

We aimed to identify all RCTs so far carried out, extending the standard search by using unconventional methods such as citation chasing and scanning of conference proceedings - methods that have proved effective in yielding additional high-quality evidence for systematic reviews and meta-analyses for other topics (Greenhalgh 2005; Vinceti 2017c). Using this approach, we identified a total of 10 RCTs that investigated monoselenium supplements for prevention of non-melanoma skin cancer, prostate cancer, any cancer, and other site-specific cancers. Overall, clear and consistent evidence indicates that selenium supplementation did not reduce subsequent cancer incidence, whether this endpoint was considered a primary or secondary outcome. Most of these trials raised concerns about possible harmful effects of selenium supplements, including increased incidence of non-melanoma skin cancer in the Nutritional Prevention of Cancer Trial (NPCT), dermatological effects in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), and type 2 diabetes in all RCTs, although with generally limited and statistically imprecise risk ratios (RRs).

Of the three liver cancer prevention trials, one reported a strongly reduced risk of liver cancer for male carriers of the hepatitis B surface antigen (HBs-Ag) taking inorganic selenium supplements (sodium selenite) for three years, and the other two studies reported little effect of organic selenium supplements (selenium yeast) for the same cancer site (Li 2000; Yu 1991; Yu 1997). Owing to several methodological concerns related to randomisation and completeness of outcome data, we judged the risk of bias as unclear for all three of these RCTs. Therefore, we could not conclude that we found strong support for selenium supplements as agents for prevention of liver cancer. Unfortunately, the other trials did not include liver cancer among their secondary outcomes, with the exception of ECOG 5597 (Karp 2013). In this RCT, investigators reported new cases of liver, gallbladder, and bile duct cancer only among selenium-treated participants; however, trial authors observed a total of only six cases, making risk estimates highly statistically unstable. In addition, the population included in this trial, which comprised patients with a history of resected non-small-cell lung cancer, was rather different from the general population.

The NPCT (NPCT 2002) reported strongly decreased risk for all cancers (-22%), and for oesophageal (-59%), colorectal (-52%), lung (-28%), and prostate (-46%) cancers, showing lesser decreases compared with the ad interim report (Clark 1996, in: NPCT 2002), but still indicative of a strong cancer preventive effect. In addition, when participants were categorised into tertiles according to baseline serum selenium, evidence suggested an inverse relationship between selenium status and effects of supplementation for all cancers and for prostate cancer in the lower two tertiles, and no effect in the upper tertile. However, interpretation of these results is difficult because in 2003, the trial authors acknowledged the occurrence of a detection bias, namely, a considerably higher rate of prostate biopsy in the placebo group, whose cause was not specified. It is unclear whether this detection bias applied only to prostate cancer or applied more generally to other outcomes (as would be the case if the bias was due to unblinding, for example). This major detection bias forced us to downgrade the reliability of this study. Data show an increase in the incidence of its primary outcome - non-melanoma skin cancer - in selenium-supplemented participants, as well as in the incidence of five other cancer types, including melanoma, bladder cancer, breast cancer, head and neck cancer, and lymphoma and leukaemia. Trial authors stated: "These results, although non-significant and based on small case numbers, may indicate potential increased risk with selenium supplementation"; these authors also relied on previous observational studies to provide some support for these positive associations (Duffield-Lillico 2002, in: NPCT 2002).

The turning point of research on selenium and cancer was the SELECT trial (SELECT 2009), a large, well-conducted prostate cancer prevention trial carried out in the male general population of North America not at high risk of prostate cancer (≤ 4 ng/mL in serum prostate-specific antigen (PSA) and digital rectal examination not suspicious for cancer). This trial, widely considered a milestone in cancer prevention and research, found no difference in prostate cancer incidence for selenium–supplemented participants as compared with placebo participants after a median follow-up of 5.5 years (hazard ratio (HR) 1.04, 95% confidence interval (CI) 0.90 to 1.18), and no effect of selenium on risk of overall cancer or on risk of other cancers (as well as cardiovascular disease). Median selenium at baseline (135 µg/L in serum in the selenium arm vs 137.6 µg/L in the placebo arm) was higher than in the NPCT (average plasma selenium 114 µg/L). The intervention used in this trial was different

from that used in the NPCT (selenomethionine in SELECT, and selenised yeast in the former), although this is unlikely to have been responsible for observed differences (Waters 2013); in both cases, the intervention comprised organic selenium species (Block 2004).

In a small study of organ transplant recipients (Dreno 2007), an unexpected increase in non-melanoma skin cancer incidence emerged; this was a matter of concern in the light of results of the NPCT. In the Polish trial Lubinski 2011, which included 1135 women with high genetic susceptibility to breast cancer due to *BRCA1* mutations, evidence was more consistent with increased risk of both all cancers and primary breast cancer than with decreased risk, although with statistically unstable HRs (1.4, 95% CI 0.9 to 2.0; and 1.3, 95% CI 0.7 to 2.5, respectively). In this trial, the intervention consisted of administration of 250 µg/d of inorganic tetravalent selenium (selenite).

More recently, results of three well-conducted phase 3 trials in participants at higher risk for prostate cancer than the general male population indicated that 200 µg/d of selenium (as selenomethionine in one study - Marshall 2011 - and as selenised yeast in the other two - Algotar 2013; Karp 2013) did not decrease subsequent cancer incidence compared with placebo. The baseline selenium status of populations included in these RCTs was comparable with that in SELECT for Southwest Oncology Group (SWOG) S9917 (135 to 138 µg/L in the two arms) (Marshall 2011), slightly lower in the Negative Biopsy Trial (NBT) (126.1 µg/L) (Algotar 2013), and unfortunately unspecified for Eastern Cooperative Oncology Group (ECOG) 5597 (Karp 2013). Results of these high-quality RCTs, all characterised by low risk of bias and two of which were discontinued before their planned end for futility, were consistent and showed no beneficial effect of selenium treatment on cancer risk.

Although not eligible for our meta-analyses because their outcome was non-malignant neoplasms rather than cancer, two recently published RCTs on colorectal adenoma risk in participants receiving selenium are worth noting. One of these trials was embedded in SELECT (Lance 2017), and the other, the SELCEL trial (an intervention study investigating the effect of selenium supplementation or celecoxib for prevention of colorectal adenoma recurrence), allocated 1374 men and women who had undergone removal of colorectal adenomas to either 200 µg/d selenium as selenised yeast, or placebo (Thompson 2016). Both RCTs did not find a beneficial effect of selenium for prevention of colorectal adenoma.

The RCTs carried out on selenium have generated clear evidence of adverse effects associated with selenium exposure, showing both the health effects related to overexposure and the amount at which these effects become evident, thus providing much more reliable evidence than that generated by environmental studies such as Vinceti 2017a for use in risk assessments of the safe upper limit of selenium exposure in humans. The trial that provided the most evidence about selenium-associated adverse effects was SELECT. These effects include an excess risk of dermatitis and alopecia, non-melanoma skin cancer, high-grade prostate cancer, and type 2 diabetes. The excess risk of dermatological effects was anticipated as a potential side effect based on previous knowledge of health consequences of human overexposure to this element (Vinceti 2001), although such effects had been predicted to occur at higher amounts of selenium exposure than those experienced by SELECT supplemented participants, thus calling for reassessment of the upper limit of selenium exposure. The increased incidence of non-melanoma skin cancer in NPCT and of advanced prostate cancer in SELECT was extremely disappointing, as they were the primary endpoints in these studies, and the expectation was that they would be reduced. The excess risk of diabetes in selenium-supplemented NPCT participants, which was also an unanticipated finding, was mostly limited to participants in the two highest tertiles of baseline plasma selenium (> 105.2 µg/L), raising concern about the safety of selenium amounts that thus far had been considered entirely safe (i.e. on the order of 200 µg/d) (Stranges 2007). Therefore, subsequent RCTs added this endpoint to monitored adverse effects that contributed to interruption of the SELECT trial, together with the null effect on cancer mortality and adverse effects of vitamin E on prostate cancer risk (Lippman 2009, in: SELECT 2009). So far, all RCTs that included diabetes among trial endpoints, including trials investigating risk of colorectal adenoma, have shown an increased incidence of type 2 diabetes among selenium-allocated participants, with RRs ranging from 1.08 to 1.71, although most estimates were statistically imprecise (Vinceti 2017b). In addition, in SELECT, a slight decrease in excess risk of diabetes in the intervention arm followed completion of selenium supplementation, further suggesting a causal relation between selenium administration and the disease (Lippman 2009 and Klein 2011, in: SELECT 2009). Currently, an excess risk of type 2 diabetes appears to be one of the adverse effects of selenium of greatest concern, and its plausibility is supported by the results of observational human studies (cohort, case-control, and cross-sectional), as well as by some biological plausibility (Galan-Chilet 2017; Su 2016; Thompson 2016; Vinceti 2015; Vinceti 2017b; Zhou 2013). These side effects, in addition to the null results of RCTs, particularly of those of the highest quality, make implementation of new trials very unlikely owing to ethical concerns.

Observational studies and aetiological association

From our meta-analyses of 16 prospective observational studies on overall cancer risk, we found lower cancer risk associated with highest selenium exposure compared with lowest exposure. Risk of cancer was 28% (95% CI 7% to 45%) lower in the highest category of selenium exposure than in the lowest, and risk of death from cancer was 24% (95% CI 3% to 41%) lower. Subgroup analyses by sex yielded increased evidence of this inverse association between selenium exposure and cancer risk in men compared with women.

The inverse association between overall cancer risk and baseline selenium levels was mainly attributable to lower risks of gastrointestinal, lung, and bladder cancer, and for men also prostate cancer. No association was seen between selenium and risk of breast cancer in women. However, when the amount of baseline exposure was taken into consideration, no clear and consistent trend between baseline selenium exposure and risk emerged for any of the major outcomes investigated in observational studies. Lack of lower risk of cancer in the highest versus the lowest selenium category among participants with the lowest baseline exposure levels compared with those with intermediate or high levels, for overall cancer, lung cancer, and prostate cancer, argues against a causal association between selenium exposure and cancer risk. This is supported by lack of a relation between differences in the highest and lowest categories of selenium exposure and the corresponding RR, further suggesting that larger differences in exposure are not associated with large and consistent decreases in RR. Finally, further uncertainty of the evidence generated by observational studies arises from the

inconsistent and sometimes sharply conflicting results on the same cancer type that emerged from different studies.

We saw little evidence of any effect of modification on the relation of selenium and cancer by geographical area of residence. It should however be noted that most of the observational cohort studies that we examined were conducted in Europe and in the USA, and none were conducted in Africa or South America. This regional distribution seems to reflect the under representation of non-Western and resource-poor countries in epidemiological research (Pearce 2004). Differential regional representation in epidemiological studies is of special interest for this review, as selenium levels in humans around the world vary significantly. Even if selenium levels measured in included cohorts reflect a broad range of naturally occurring selenium exposure, investigators have reported some of the lowest and highest levels of selenium exposure in populations from South America (Jaffé 1992), Africa (Hurst 2013b), China (Li 2012), and India (Chawla 2016) - regions not investigated by any of the reviewed observational studies, with the exception of three Chinese trials. Concerning sex-related effects, our meta-analysis of longitudinal studies revealed an inverse association between RR of cancer and selenium status in some cases in men but not in women for the same cancer type. Unfortunately, although more than half of reviewed studies included mixed-sex populations, most did not report sex-disaggregated results. In available sex-specific results, men are over represented - a fact that may potentially hamper assessment of the relation between selenium exposure and cancer risk in women. Theoretically, factors such as variations in body composition between men and women, including lean body mass versus fat composition, or differences in metabolism or in nutritional requirements (e.g. higher antioxidant requirements, particularly for the urological system) between the two sexes might be associated with differential effects of selenium for prevention of cancer.

Concerning the indicator used to assess selenium exposure and its relation with cancer risk, we observed generally null associations when evaluating selenium status through assessment of dietary intake, although some inverse associations at specific cancer sites emerged when we used biomarkers such as blood or toenail selenium levels. We extensively reviewed in the previous version of this review the characteristics and limitations of indicators of selenium exposure, with particular reference to dietary assessment methods and biomarkers, and inconsistencies across studies assessing the validity of different indicators (Ashton 2009; Fairweather-Tait 2011; Jablonska 2015a; Vinceti 2014). In particular, a large body of literature concerns the limitations of dietary assessment methods, mainly linked to large variations of selenium content in single food types, and the limitations of biomarkers of exposure. Concerning the latter, a major source of exposure misclassification consists of the different behaviours of inorganic and organic selenium species, whose tendency to be retained in the body and to accumulate in specific body tissues greatly varies, although this does not necessarily correlate with their biological activity (Behne 1996; Behne 2010; Kim 2001; Michalke 2017; Panter 1996; Slavik 2008; Solovyev 2013; Steen 2008; Tiwary 2006; Vinceti 2013c). Investigators have frequently proposed that selenoprotein activity may be an indicator of selenium status and may be tested in association with cancer risk (Vinceti 2017b), but this relation has been questioned because different sources of oxidative stress, paradoxically including pro-oxidant selenium species themselves, may upregulate selenoprotein activity (Jablonska 2015a). Furthermore, intake of heavy metals and other dietary factors such as vitamins, metalloids, and amino acids (e.g. methionine) may modify the health effects of selenium, or the relations between selenium exposure and biomarkers (Jablonska 2015a; Vinceti 2000), owing to metabolic interactions or changes in tissue-specific deposition and retention of selenium (Behne 1996; Zeng 2005; Zwolak 2012).

Overall, available evidence indicates the potential for exposure misclassification in observational studies on selenium, as well as the pitfalls associated with an approach based on assessment of total selenium content in peripheral biomarkers, suggesting that in some instances, measurements of nutritional intake might provide better exposure estimates than are provided by biomarkers, particularly in the light of relative exposure to inorganic and organic species of the element. In general, observational cohort studies on selenium and cancer are expected to have been characterised by random exposure misclassification, thus shifting RRs towards the unity and reducing the ability to detect real associations. However, some exposure misclassification may have been non-random, such as that induced by smoking, which although it is a source of selenium exposure also induces lower body selenium levels, possibly owing to an effect of cadmium in increasing selenium excretion (Vinceti 2000). In such cases, exposure misclassification based on biomarkers (serum/plasma selenium levels) may have substantially biased risk estimates and may have been associated with some degree of confounding due to the well-known effect of smoking on cancer risk, which could not have been adequately captured and controlled for. Inadequate control for smoking has been suggested to be a major confounder inducing spurious associations between low selenium levels and enhanced cancer risk in observational studies (Beane Freeman 2015).

In addition to exposure misclassification, and probably more important than this, a major issue affecting observational studies is unmeasured confounding (Vinceti 2016a). This potential bias is a matter of greater concern than exposure misclassification because it may have systematically biased RRs in one direction, particularly for some cancer types. Moreover, detection (and control) of this bias is extremely difficult and nearly impossible, given the hundreds of nutritional and non-nutritional lifestyle variables that may be associated with both variations in selenium intake and cancer risk. Among these factors are smoking (Beane Freeman 2015; Vinceti 2013b), socioeconomic status - which appears to be positively associated with socioeconomic position in both men and women (Gundacker 2006; Niskar 2003) -and most likely hundreds of nutritional and toxicological factors that may vary in the diet, together with selenium intake. An approach that would reduce the risk of unmeasured confounding in observational studies might include investigation of dietary patterns rather than single nutrients, but these investigations seem not to have made adjustments for diet quality. Finally, it should be noted that most studies did not take into account the role of genetic factors (related to selenoproteins or otherwise) in the relation between selenium exposure and cancer risk, although some studies have suggested the importance of such relations (Jablonska 2016; Meplan 2014); the true relevance of genetic factors has not yet been well defined. Some studies examining selenoprotein-related single-nucleotide polymorphisms have suggested a role for genetic variants among genes coding for selenoproteins in modifying cancer risk, or in determining the relation between selenium

exposure and subsequent cancer risk, although results have not been consistent (Geybels 2013; Meplan 2012; Penney 2010; Penney 2013; Slattery 2012; Takata 2011).

With awareness of the fundamental limitations of observational studies, even of those of longitudinal design, which may avoid selection bias or reverse causality, investigators designed and carried out in the 1990s and the 2000s several experimental studies as RCTs investigating the effect of selenium supplements on cancer risk. The evidence base from these intervention studies has become so large and complete as to allow a comprehensive evaluation of cancer risk associated with selenium supplementation for some specific cancer types. It is interesting to note that major interest in the cancer preventive activity of selenium originated not just from observational studies (mainly of ecological and cohort design) (Vinceti 2013b), but from a randomised trial - the ad interim analysis of the NPCT, which was published in 1996 and attracted great interest from both the scientific community and the general public because of the apparently large beneficial effect that it reported (Clark 1996, in: NPCT 2002). Null results of the most recent low-bias RCTs - Algotar 2013; Marshall 2011; SELECT 2009 - also do not suggest a major or strong role of genetic factors in modifying selenium and cancer relations, given their generally null or troubling results. An exception can be seen in recent data from SELECT, which suggest that a genetic variant of the NKX3.1 androgen-regulated prostate tumour suppressor protein may modify, or increase, the risk of prostate cancer associated with selenium supplementation (Martinez 2014).

From a methodological perspective, we acknowledge that comparison of risks between highest and lowest exposure categories in observational studies, as performed in the present meta-analysis, is most suitable for identifying an effect when a consistent decrease or increase is seen across absolute exposure levels. Other associations (e.g. threshold effects, U-shaped relations) may have been missed by this method of meta-analysis, or their true effect might have been diminished.

Overall completeness and applicability of evidence

RCTs and preventive efficacy

This review investigated a diverse range of cancers, substantially extending the analysis compared with that performed in previous reviews. However, cancer is not a uniform condition, and malignant neoplasms show great differences in tumour biology. Only non-melanoma skin cancer, liver cancer, and prostate cancer have been investigated as primary outcomes in the included prevention trials, and, regarding these main outcomes, specific characteristics of study populations may limit the generalisability of results. Participants in included RCTs on skin and liver cancer belonged to populations at high risk for the outcome under investigation, and participants in high-quality prostate cancer trials were at average risk (Karp 2013; SELECT 2009), or at high risk (Algotar 2013; Marshall 2011), for this disease. Most participants in the NPCT were older and white, predominantly male inhabitants of the United States, and the most recent trials were limited to the USA male population.

Average baseline selenium exposure in the NPCT was less than that characterising subsequent trials carried out in the United States, although it was more similar to that seen in some European populations. Although the NPCT suggested that selenium supplementation was beneficial only at the lowest range of baseline selenium exposure, the most recent studies, carried out in populations generally characterised by higher average selenium exposure, did not confirm such an interaction. The NPCT also found an indication of strong effect modification for sex, as demonstrated, for example, by the HR for all cancers associated with selenium supplementation - 0.67 (95% CI 0.50 to 0.89) in men and 1.20 (95% CI 0.66 to 2.20) in women (NPCT 2002).

Participants in the SELECT study on prostate cancer prevention were apparently healthy men over 50 years of age from the general population of North America (SELECT 2009). A large sample size and inclusion of non-white participants from different socioeconomic backgrounds support the generalisability of study findings to other adequately nourished populations.

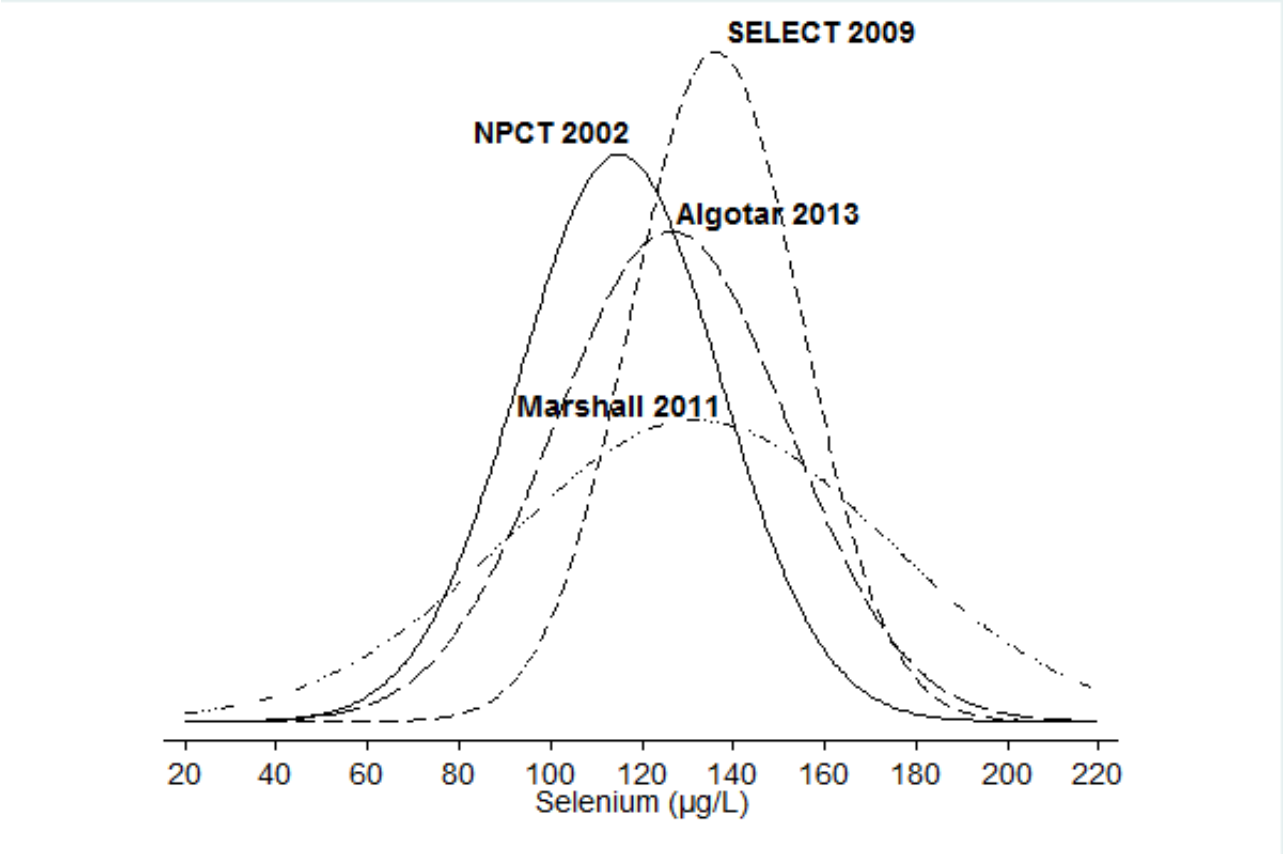
Selenium supplements generally contain organic or inorganic species of selenium, or a mixture of both (e.g. in the form of selenised yeast). Different species of selenium may exhibit different effects on human health and more specifically on proteomic endpoints, as also suggested by human controlled randomised trials though with inconsistent results (Ravn-Haren 2008; Richie 2014). High-quality RCTs using selenised yeast supplements, almost entirely comprising organic selenium forms (Block 2004; Waters 2013), found no effect of supplementation on the main study outcome and an indication of a harmful effect (i.e. an excess diabetes risk) (Vinceti 2017b). The SELECT trial used supplements of L-selenomethionine, which is the major component of selenised yeast, and also found no preventive efficacy. The only two RCTs investigating sodium selenite supplements found a protective effect against liver cancer, and null or adverse effects on breast cancer risk, but we considered these trials to have unclear risk of bias. It is unclear how applicable these results are in other settings and in populations with a different nutritional status. Interpretation of the results of clinical trials using selenium supplements should consider the different chemical forms of selenium, as well as their potentially different health effects when used as supplements (Vinceti 2013c; Weekley 2013). Most studies used organic selenium as selenised yeast (Algotar 2013; NPCT 2002), or as selenomethionine (Marshall 2011; SELECT 2009). However, the chemical form used is unlikely to explain the differences in results between NPCT and the other trials (Waters 2013). With reference to this issue, of interest are the results of a 'natural experiment' that occurred in Northern Italy, wherein a small population unintentionally consumed for several years drinking water with an unusually high content of selenium in its inorganic hexavalent form - selenate (Vinceti 2000). Follow-up of that population revealed increased risk of neurodegenerative disease - a not entirely unexpected finding owing to the potential neurotoxicity of inorganic selenium (Vinceti 2014a), along with a slightly increased risk of cancer, mainly due to excess risk of oropharyngeal cancer, melanoma, kidney cancer, and lymphoid malignancies (Vinceti 2016b).

An important issue is the possibility that participants with low baseline selenium status may experience an inverse association between selenium exposure and cancer risk, as suggested by some trial authors (Lu 2016; Rayman 2009). This has been suggested to explain the different results of SELECT and the NPCT, and could also hypothetically explain, at least in part, the different relations found in experimental as compared with observational studies. NPCT found a strong beneficial effect of selenium supplementation among participants at the lowest tertiles of baseline selenium

levels; however, the risk of cancer changed abruptly from an apparently protective effect in the two lower tertiles (HR 0.51 and 0.70) to an excess risk in the highest tertile of plasma selenium (HR 1.20, 95% CI 0.77 to 1.86). This occurred despite a difference of only 16.4 µg/L between lowest and highest tertiles, corresponding to a change in dietary selenium intake as low as around 10 µg. This would imply that such a small a change in selenium dietary intake would change a strongly protective effect of the element on cancer risk into a possibly detrimental effect - an implausible scenario given the wide range of selenium intake (from about 20 to several hundred micrograms) characterising Western populations. Moreover, the intermediate tertile of baseline plasma selenium in the NPCT (105.6 to 122.0 µg/L) appeared to be associated not only with reduced overall cancer risk but also with an excess risk of squamous cell skin carcinoma (HR 1.49, 95% CI 1.05 to 2.12) and overall non-melanoma skin cancer (NPCT 2002), as well as diabetes (RR 1.36, 95% CI 0.60 to 3.09), whose risk also considerably increased at the highest tertile of baseline selenium (Stranges 2007). Overall, this occurrence of both adverse and beneficial effects is unlikely if the selenium supplementation was serving to remedy a selenium deficiency. In addition, the strongest effect of selenium on overall cancer risk at lower levels of baseline selenium status was due to a considerable decrease in prostate cancer, but this finding was subject to detection bias because of a decreased biopsy rate in selenium-supplemented participants, particularly in those with lowest baseline selenium status, as recognised by investigators of the NPCT (NPCT 2002).

In addition, after NPCT, three of the four high-quality RCTs on selenium supplementation for cancer prevention investigated the possible modifying effect of baseline selenium exposure and found no evidence of a beneficial effect of the intervention even in the lowest baseline exposure category. For instance, in NBT (Algotar 2013), the average baseline plasma selenium level at the lowest tertile of the study population was 101.1 µg/L - much lower than the corresponding level at the middle tertile of NPCT (114.6 µg/L), in which the HR of prostate cancer had been as low as 0.33 (95% CI 0.13 to 0.82). However, in this 'low' NBT subgroup, investigators found no evidence of a beneficial effect of selenium supplementation on prostate cancer risk. In the SWOG S9917 trial (Marshall 2011), data show no change in the null effect of selenium in the two lowest categories (quartiles) of selenium intake, whose boundaries were < 106 and 106 to132 µg/L - similar to cut points of the two bottom NPCT tertiles and of the bottom category of NBT. In these two subgroups of the SWOG population with the lowest baseline selenium status, the RR of prostate cancer was 0.82 (95% CI 0.40 to 1.69) and 1.38 (95% CI 0.68 to 2.78), and in the third upper quartile, the RR was 0.98 (95% CI 0.58 to 1.68), suggesting no consistent trend of an inverse relation between antecedent selenium exposure and effects of supplementation (as was also shown by analysis for trend in this study). Investigators in SELECT reported no reduction in cancer risk among selenium-supplemented participants, although they did not provide specific RRs according to baseline selenium status. Calculation of blood selenium content distribution in SELECT, as well as in the three other RCTs (NPCT, NBT, SWOG), showed substantial overlap of plasma and serum selenium levels between this large trial population and the other study populations (Figure 7). In addition, a more recent case-cohort study carried out within SELECT assessed the effect of selenium supplementation on prostate cancer risk, taking into consideration baseline selenium exposure, as assessed through toenail selenium levels. The study, which involved 1739 prostate cancer cases and 3117 controls, was unable to find a beneficial effect of selenium supplementation in the lowest categories (quintiles) of baseline toenail selenium (Kristal 2014). Actually, a dose-response effect in that SELECT population emerged, but it favoured an increased risk of (high-grade) prostate cancer induced by selenium supplementation among participants belonging to the two upper quintiles of baseline selenium exposure (Kristal 2014). Therefore, it seems reasonable to agree with this SELECT statement: "The analysis of our data using lower cut points for baseline toenail Se categories, in an attempt to replicate findings from the NPCT, also showed no evidence of benefit from supplementation among men with low baseline Se status (data given in Results). Given these findings, we believe it reasonable to conclude that Se supplementation of men at the low range of Se intake common in USA men will not reduce PCa risk" (Kristal 2014).

Figure 7. Baseline circulating selenium levels in the NPC trial (Duffield-Lillico 2003b in: NPCT 2002), the NBT (Algotar 2013), SWOG trial (as plasma selenium) (Marshall 2011), and SELECT (as serum selenium) (Lippman 2009, in: SELECT 2009). When median and interquartile values were reported, we estimated mean and standard deviation according to Cochrane guidelines provided in Higgins 2011a.



Overall, results of recent high-quality RCTs do not support the hypothesis that differing baseline selenium status may explain conflicting results between NPCT and SELECT (Lu 2016; Rayman 2009). Results of the most recent RCTs seem therefore to be applicable to populations with various degrees of background selenium exposure, with the exception of populations characterised by extremely low (< 20 µg) or high selenium intake.

Observational studies and aetiological association

We reviewed data from prospective observational studies in which investigators measured selenium exposure in populations without evidence of cancer, who were then followed up for a specified period of time. We limited our systematic review to cohort studies to avoid or decrease two major sources of bias in observational investigations, particularly in case-control and cross-sectional studies (i.e. selection bias and risk of reverse causality). Data continue to show important differences among included studies in terms of selenium exposure assessment, types of outcomes, and study populations, which may affect their interpretation. The small number of studies that examined most of the meta-analysed types of cancers prevented a thorough investigation of sources of heterogeneity between study results. In particular, we had limited opportunity to explore the influence of specific sources of bias or the methodological quality of epidemiological studies on heterogeneity.

Participants examined in this review update include more than 2,300,000 individuals, predominantly from Europe and North America, and, to a much lesser extent, from Asia and Australia. We were able to identify no prospective observational studies on selenium and cancer risk from Africa or South America. This regional distribution reflects the under representation of non-Western and resource-poor countries in epidemiological research (Pearce 2004). Differential regional representation in epidemiological studies is of special interest for this review, as selenium levels in humans around the world vary significantly. Selenium levels measured in the included cohorts reflect a broad range of naturally occurring selenium exposure, as documented by several epidemiological studies worldwide. However, some of the lowest and highest selenium levels in humans have been reported in populations in South America (Jaffé 1992) - a region not investigated by any of the reviewed observational studies.

More than half of the included studies enrolled mixed-sex populations, but most did not report sex-disaggregated results. In available sex-specific results, men are over represented - a fact that could hamper potential assessment of the relation between selenium exposure and cancer risk in women. Despite this sex imbalance, we systematically saw stronger (inverse) associations with cancer risk among men than among women, for whom such associations with antecedent selenium status was nearly absent. This was true for stomach, colorectal, and lung cancer, and, when

added to the inverse association for prostate cancer, led to an impact on overall cancer risk that was clearly lacking in women that could be due to potential confounders (such as smoking, occupational exposures, or other dietary factors) or to a real change in the association between selenium exposure and cancer risk in the two sexes.

The range of selenium exposure experienced by members of cohorts investigated in the observational studies was generally lower than that experienced by participants in RCTs, who added supplemental selenium, generally 200 µg/d and in its organic forms, to their usual background intake, which ranged from about 70 to 90 µg/d as organic selenium, although some RCTs provided no estimate (Jablonska 2015a). It is theoretically possible that a preventive effect of selenium against cancer exists only at low (< 30 to 50 µg/d) intake of the element, and that it disappears at higher intakes, when 'saturation' or 'maximisation' of selenoprotein expression driven by selenium occurs. Investigations have frequently chosen this proteomic endpoint as a reference point for deriving dietary reference values for selenium (Jablonska 2015a; Vinceti 2017a). Selenium exposure in the range of around 50 to 200 µg of daily selenium intake has not been tested by intervention studies, which have used larger amounts of supplemental selenium, and is unlikely to be tested in RCTs in the future, given the termination of past trials for futility or safety concerns. This possibility must be considered, but within the context of the two fundamental limitations of observational studies - exposure misclassification and unmeasured confounding, which limit the reliability of the evidence they generate and its applicability in terms of cancer prevention.

A few lines of evidence suggest that even at low levels of selenium exposure, it is unlikely that such an inverse association with cancer risk exists. First, inconsistencies in the results found in our meta-analysis for most cancer sites and lack of a dose-response relation between cancer risk and selenium at varying levels of background selenium exposure, or of a difference between highest and lowest exposure categories, argue against a real relation between selenium and cancer risk. Limited differences between highest and lowest categories of selenium intake, often amounting to a difference of only 20 to 30 µg per day, compared with large variations in selenium intake worldwide (from 10 to 15 µg in low-selenium areas up to several hundred µg in seleniferous areas), also argue against a true relation. Finally, as previously described, some recent high-quality RCTs investigated the effect of baseline selenium status on cancer risk associated with selenium supplementation and found no beneficial effect of selenium supplementation, even among participants with the lowest amounts of baseline exposure. Overall, these findings do not support an association between higher selenium status and lower cancer risk independently from factors such as sex, baseline selenium exposure, and cancer type. One additional observational cohort study, which could not be meta-analysed in this review because it was released in PubMed in July 2017, appears to confirm these conclusions (Sandsveden 2017).

Quality of the evidence

RCTs and preventive efficacy

SELECT (SELECT 2009), SWOG S9917 (Marshall 2011), NBT (Algotar 2013), and ECOG 5597 (Karp 2013) were the only trials considered to have low risk of bias with adequate sequence generation, allocation concealment, blinding, and reporting of findings, and the consistency of their findings for prostate cancer, as well as for other cancer types for the two trials investigating them (SELECT and ECOG 5597), added to the statistical power of the major trial (SELECT), making their overall results highly reliable and suitable for yielding useful evidence to assess the relation between selenium supplementation and cancer prevention. These trials are also of major importance because (with one exception) they have provided information about baseline selenium exposure and its possible modifying role and about the effect of selenium supplementation on subsequent cancer incidence. Another important feature of these trials has been their ability to address the issue of selenium overexposure and related adverse effects owing to a systematic surveillance system for adverse effects, as well as their ability to extend the monitoring programme to additional effects, if suggested by new analyses targeting previously unplanned secondary endpoints, as was the case for diabetes (Stranges 2007). This is particularly relevant because all of these trials were planned under the hypothesis, later found to be erroneous but at that time endorsed by regulatory agencies, that the supplemental selenium dose administered to intervention arms (200 µg/d in almost all RCTs) was entirely safe and was well below the upper safe limit of the element, even with consideration of background selenium exposure.

These trials may continue to yield important results. Secondary analysis of additional endpoints, or based on genetic and non-genetic biomarkers of exposure to selenium and other factors, is still possible. For example, major contributions were yielded by SELECT in 2017, concerning outcomes such as prevention of colorectal adenoma and of Alzheimer's disease by selenium supplementation, in both cases with null results (Kryscio 2017; Lance 2017).

We assessed the certainty of evidence from high-quality RCTs using the GRADE approach (http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.svwngs6pm0f2) and reported the results of this assessment in the 'Summary of findings' table (Summary of findings for the main comparison). From preliminary assignment to a high level of certainty due to the experimental study design, we did not identify reasons to downgrade trial quality according to standard GRADE guidelines for risk of all cancers, for risk of cancer mortality, or for risk of colorectal, lung, bladder, or prostate cancer. In contrast, meta-analysis for breast cancer risk yielded a statistically imprecise result mainly reflecting the small number of cases, and meta-analysis for non-melanoma skin cancer showed high statistical heterogeneity across studies. When addressing factors possibly increasing the certainty of evidence assessment, we considered as non-applicable the GRADE item "*All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed*", neither could we evaluate possible dose-response gradients because unfortunately they were not tested in these RCTs. We therefore rated the certainty of evidence as 'high' if it indicates no effect of selenium supplementation on all cancers overall, on cancer mortality, nor on colorectal, lung, bladder, and prostate cancer, and we considered certainty of the evidence as 'moderate' if it indicates no effect on non-melanoma skin cancer and breast cancer, with downgrades due to heterogeneity and imprecision, respectively. However, stating that the evidence supporting no effect of selenium on cancer prevention at these sites is of moderate rather than high certainty does not mean that the only alternative hypothesis is

necessarily that selenium decreases risk of cancer at these sites. Actually, the overall results of high-quality RCTs, when available, suggest a slight to moderate although statistically imprecise increase in the risk of some of these specific cancers following selenium supplementation.

Concerning the RCTs that we downgraded in our appraisal of risk of bias, we considered the quality of reporting to be an issue in the three trials on liver cancer prevention, thus leading to their classification as having unknown risk of bias. Several papers reported the individual trials, in some cases discrepantly, and essential questions regarding sequence generation, allocation concealment, handling of dropouts and withdrawals, and detection of outcomes remain unanswered. This might be due to inadequate reporting but might also hint at flaws in trial design and implementation. We were uncertain about whether the only trial that reported positive results for selenium supplements in liver cancer prevention randomly assigned participants individually. Cluster randomisation of participants who lived in the same area/village, which may have been the procedure used in this investigation, might have introduced additional bias to the study results (e.g. as the result of different environmental factors contributing to liver cancer development or detection) and might have led to an overestimation of the protective efficacy of selenium. Duplication of results of trials based on a rigorous study design would be necessary to assess the effects of sodium selenite on liver cancer incidence. With regard to the NPCT (NPCT 2002) and the trial of Dreno 2007, indications of serious detection bias for the USA study and of unclear methodological details (such as blinding) for the French investigation led us to consider these experimental studies to be at unclear risk of bias, as discussed in greater detail elsewhere in this review. As far as the trial on breast cancer is concerned (Lubinski 2011), our downgrade of evidence certainty was based on incomplete information provided in the only report that we could retrieve (an abstract), although we acknowledge the relevance of that trial - the only trial specifically targeting breast cancer and a genetically specific population - and the fact that complete reporting of trial procedures may lead to reassessment of trial quality and its upgrade.

Observational studies and aetiological association

The 70 observational studies were heterogeneous, not only in methodology, but also in the quality and level of detail of reporting and in their potential biases. We assessed our confidence in the evidence from these studies using the GRADE approach and reported our findings in Summary of findings 2; we reported judgements only for those outcomes evaluated in the 'Summary of findings' table for RCTs with low risk of bias.

Confounding and other biases

Selenium measurement and exposure misclassification

All studies on total cancer risk identified cases by using registry links or a combination of several methods, and losses to follow-up were generally very low. One study on cancer incidence and two studies on cancer mortality analysed less than 80% of all identified cases (incidence: Coates 1988: 79%; mortality: Kok 1987a: 71%; Kornitzer 2004: 57%). The main reason for this loss of sample was missing selenium measurements. Not all studies that assessed mortality as a measure of cancer risk excluded people with cancer at study inception. This might have led to overestimation of a protective effect if selenium levels were lowered by the presence of cancer. We therefore consider the results for cancer incidence to be more valid than the cancer mortality results.

Concerning the outcome most frequently investigated - prostate cancer - all but two of the included studies identified cases by using links to cancer registries or a combination of personal follow-up interviews with PSA screening. Two studies with health professionals used self-reporting for case identification, followed by confirmation through medical records. The number of people lost to follow-up was low in all included studies. However, two studies included less than 80% of all identified cases in their analyses because samples were not available for selenium measurement, or diagnosis was not confirmed (Brooks 2001: 39%; van den Brandt 2003, in: van den Brandt 1993: 77%). In Brooks 2001, bias might have been introduced to the results to some extent, as demographic variables differed between identified and analysed cases.

Residual confounding and effect modification

Most of the included studies used controls for smoking and age by matching or using multi-variate techniques. However, the control for self-declared smoking habits may be inadequate, and this may occur particularly in people with a diagnosis of cancer (Connor Gorber 2009; Gerritsen 2015; Morales 2013). Control for smoking as a known risk factor for several types of cancer is an important issue in epidemiological studies on cancer risk, and inadequate control for this cancer risk factor has been recognised as a major methodological issue affecting observational research on selenium and cancer (Beane Freeman 2015). This possible bias may be particularly relevant for research on selenium biomarkers and cancer. Cigarette smokers tend to have lower selenium biomarker levels, although cigarette smoking in itself is a source of selenium exposure. In addition to this source of non-random exposure misclassification, it is well recognised that smoking is a powerful cancer risk factor, thus qualifying it also as a major confounder when the selenium and cancer relation is investigated. Therefore, an inverse association between low baseline selenium status and lung cancer risk might be the result of residual confounding and effect modification by smoking, and this may also be true for other cancer types (Beane Freeman 2015). Exposure to environmental and household smoking, which has been shown to be associated with increased risk of cancer (Gorlova 2006; Nishino 2001), might be associated with selenium status due to differential nutritional behaviours or other mechanisms.

Several other factors may act as effect modifiers or confounders. Possible confounding factors could consist of another food nutrient or a certain behaviour that exhibits cancer protective effects and may be associated with higher intake of selenium-rich foods. The number of candidates for such a role is so large that no observational study can measure all of these factors nor account for them. Furthermore, it is well known that intake of heavy metals (such as arsenic, cadmium, and mercury) and other dietary factors such as methionine may substantially modify selenium health effects or relations between selenium exposure and biomarkers (overview, in: Vinceti 2000; Zeng 2005; Zwolak 2012), and may potentially confound the association between selenium and cancer.

Some potential confounders cluster in population groups according to socioeconomic position (SEP), and this factor has been shown to vary together with selenium status in both men

and women (Gundacker 2006; Niskar 2003). Only a few studies attempted to control for indicators of adult SEP as potential confounders (e.g. education, occupation, income). None used a composite index of indicators or considered childhood SEP. Some studies restricted their cohorts to certain subgroups of a population, such as occupational groups, and were likely to include only people of a similar adult socioeconomic background.

It has been claimed that associations between vitamins and diseases are the result of confounding by social and behavioural factors acting over the course of a lifetime (Lawlor 2004). Lawlor 2004 argued that divergent results from epidemiological and randomised controlled studies on prevention of cardiovascular disease can be explained by unmeasured confounding due to SEP. Risk of most cancers is known to decrease with higher SEP. Research also indicates a positive association between higher SEP and selenium biomarkers (Barany 2002; Niskar 2003). However, other investigations have not confirmed these findings: Kant 2007, for example, did not find an association between a measure of household poverty and selenium status.

The hypothesis of possible confounding due to SEP leading to an indirect association between selenium and cancer would be consistent with results of observational studies for all types of cancers in this review, with the exception of prostate cancer. Dalton 2008 found that prostate cancer has been diagnosed more often in men of a higher SEP, and we saw a protective association of higher selenium exposure with this cancer type. It remains unclear whether the more frequent diagnosis of prostate cancer in men with a higher SEP actually reflects an excess of prostate cancer incidence in this population. It might also result from differential health and screening behaviours leading to detection of otherwise symptom-free cases, while men with a lower SEP tend to be over represented in diagnoses of the disease at advanced stages (Rapiti 2009). More information on screening and diagnostic behaviours of male cohort participants would be necessary to further elucidate these issues.

Another consideration is genetic factors, which may both confound and modify the role of selenium in cancer prevention and causation. Recent observational studies examining selenoprotein-related single-nucleotide polymorphisms have suggested a role for genetic variants in genes coding for selenoproteins or other proteins in modifying cancer risk, or even the relation itself between selenium and cancer risk, although results have not been consistent (Gerstenberger 2015; Geybels 2013; Jablonska 2015b; Meplan 2015). Null results of the most recent low-bias RCTs do not suggest that at least the most frequent genotypes strongly influence the selenium and cancer relation (Algotar 2013; Marshall 2011; SELECT 2009), although such hypotheses cannot be ruled out for more rare genetic variants of selenoproteins or other proteins. Hypothetically, different genetic factors could increase and decrease the risk of cancer associated with selenium exposure, cancelling each other out and resulting in an overall null effect. Additional data from SELECT based on genotyping of study participants, if available, might be extremely useful for assessing hypotheses regarding genetic variants of selenoenzymes and their interaction with selenium status. So far, the only evidence derived from SELECT indicates that single-nucleotide polymorphisms related to the prostate tumour suppressor protein *NKX3.1* gene (CC genotype at rs11781886) may increase cancer risk following selenium supplementation (Martinez 2014). Recent observational evidence also suggests that polymorphisms of selenoproteins and other antioxidant proteins in men with non-metastatic prostate cancer may be associated with increased risk of high-grade disease and subsequent prostate cancer recurrence (Gerstenberger 2015).

Summary

In observational studies, factors that may have accounted for inter-study heterogeneity and that may have biased study results include type of outcome measure, exposure assessment, sex, incomplete control for confounding (smoking and socioeconomic position), and unmeasured confounding, linked to both dietary and non-dietary factors. Given the high risk of bias due to these factors, particularly to the unmeasured confounding inherent in observational studies, along with conflicting results of several studies and lack of any modification of the selenium and cancer relation by level of baseline selenium exposure and by the difference between highest and lowest selenium categories, we consider the evidence provided by observational studies to have very low certainty (Summary of findings 2); therefore these results must be interpreted with great caution and do not allow firm conclusions about a possible cancer-preventive effect of selenium intake. Meta-analyses of spurious findings in observational studies enhance the precision of a summary risk estimate, which does not itself get nearer to the true value and may suggest a non-existent association (Egger 1998).

Potential biases in the review process

RCTs and preventive efficacy and observational studies and aetiological association

The literature search included major international databases in the English and German languages, and we applied a broad search strategy supplemented by handsearching for references. We assume that we identified all randomised controlled studies and prospective observational studies relevant to our review questions. As we did not search databases in other languages (e.g. Chinese, Russian), we cannot rule out that we might have missed smaller studies that were not published in international journals. However, we consider it unlikely that we could have missed major sources of evidence through our approach. We also might have missed observational studies whose results on selenium exposure and cancer were reported in the body of a paper but were not mentioned in the paper's title or abstract, even if the paper is indexed in the searched databases. However, our systematic use of backward and forward citation chasing and our search for relevant abstracts in conference proceedings or related material should have substantially decreased the risk of missing literature that could have been relevant for our assessment.

When needed because of lack of complete or appropriate participant data (e.g. when cohorts including cancer and non-cancer participants were mixed in data analysis), we contacted study investigators to ask for data missing from their studies. We also did this when we did not have enough data from published reports to adequately appraise study risk of bias. Sometimes we were unable to obtain answers to questions that we had regarding methods or outcomes, but frequently investigators kindly gave us the information we needed. We were sometimes unable to obtain answers, particularly for earlier epidemiological studies from which primary investigators may have relocated or died, or we found that data were not available in a current electronic format. Similarly, we could not make contact with primary investigators of Chinese RCTs.

We based our risk of bias assessment on information included in the original publications, unless the trial authors that we contacted gave us additional details. This means that in some instances, we may have overestimated the true risk of bias of studies that did not adequately describe their design in the original publications, such as Lubinski 2011.

Another concern, especially with epidemiological studies, is publication bias. Cohort and nested case-control studies often are not exclusively designed to test for a specific exposure-outcome association but enable investigators to investigate a range of questions. It is conceivable that unfavourable results were less likely to be published, although we could not find evidence supporting such a hypothesis. Our analysis of this issue through use of a funnel plot gave some support to publication bias for prostate cancer.

We systematically meta-analysed RCTs even when only two studies were available (Karp 2013; NPCT 2002). Finally, we carried out two meta-analyses of intervention studies - one on all studies, and another on RCTs assessed through a standard appraisal tool as being at low risk of bias - and we emphasised results of the latter, as derived from high-quality experimental studies. For observational studies, we decided a priori to conduct meta-analyses only when five or more studies were available for a study outcome, thus excluding from meta-analysis the few endpoints for which up to four studies were available (Table 1). Our primary intention was to facilitate the investigation of heterogeneity between studies included in meta-analyses, to avoid producing more precise, but still unexplainably biased, results. However, our emphasis was clearly given to experimental studies because this trial design is widely recognised as the only one that may provide convincing evidence of an association between a factor and disease risk, or more generally biological endpoints, and this may be particularly true in nutritional epidemiology (Vinceti 2016a).

Finally, the authors of this review, as already noted in the previous version of the review, came from different disciplines and have different areas of focus (e.g. epidemiology, biostatistics, clinical medicine, nutrition). We continue to consider such variety of expertise to be a strength of this review, and we made use of it by applying multiple checking procedures during the entire review process whenever possible.

Agreements and disagreements with other studies or reviews

Recent reviews that have investigated the relation between selenium and cancer prevention have generally concluded that this trace element has no clear beneficial effect(Bjelakovic 2012; Cortes-Jofre 2012; Cui 2017a; Fortmann 2013; Kushi 2012; Moyer 2014; Posadzki 2013; Schwingshackl 2017), although updated systematic reviews and meta-analyses on selenium encompassing all of the most recent intervention studies are lacking. These results are true for both all cancers and prostate cancer, and for other specific cancers, such as lung cancer. The turning point in the evaluation of the effect of selenium on cancer risk is generally acknowledged to have been SELECT, and the other trials, although their findings are consistent with SELECT, have received less attention, probably mainly because of their smaller size. It is understandable that most of the selenium trials under way during the 2000s and the 2010s and originally implemented mainly as the result of the promising results of the original NPCT, particularly its ad interim 1996 report, were eventually discontinued owing to the results of SELECT (which was discontinued too) and the null results of ad interim futility analyses (Vinceti 2017b). This seems also to be true for Brodin 2015, Chen 2013, and Vinceti 2017a - planned RCTs on the possible utility of selenium for cancer therapy - and is an issue of considerable interest that has been investigated so far in very few phase 2 and phase 3 trials (Goossens 2016; Karamali 2015; Muecke 2014; Stratton 2010) (although other trials appear to be under way such as Vinceti 2017b).

Concerning observational studies, very few recent reviews have investigated the selenium and cancer relation, and they have focused on only a few cancer sites. These reviews have generally yielded results consistent with ours. For prostate cancer, a recent review found no association between baseline serum selenium and risk in cohort studies (Cui 2017b), as was reported by Allen 2016, which conducted a pooled analysis using individual data from 15 cohort studies. However, in the latter review, baseline serum selenium status was determined to be inversely associated with high-grade prostate cancer risk, as was toenail selenium and subsequent prostate cancer incidence. Gong 2016 also found reduced risk of gastric cancer among participants in the highest baseline selenium exposure category. Other reviews and meta-analyses considered other cancer types such as liver, pancreatic, lung, and breast cancer, but these reviews generally incorporated case-control and cross-sectional studies in addition to cohort studies, further increasing the risk of bias due to heterogeneity of study designs. Most reviews on observational studies have acknowledged the key methodological issues noted in this type of study, namely, risk of unmeasured confounding and potential biases associated with this limitation.

AUTHORS' CONCLUSIONS

Implications for practice

A large body of evidence is now available from high-quality randomised controlled trials on effects of selenium supplementation on cancer risk, with two new studies published since the last version of this review (Vinceti 2014). None of the new relevant studies have provided information to change the conclusions of the previous version of this review. Overall, results of these studies have consistently shown no effect of selenium in preventing the type of cancer most consistently and strongly associated with antecedent selenium exposure - prostate cancer - or in preventing cancer overall, even when assessment focused on participants with the lowest selenium status at baseline. These intervention studies have suggested that selenium administration on the order of 200 µg/d increased risk of non-melanoma skin cancer, advanced prostate cancer (in individuals with highest baseline exposure), dermatological abnormalities, and type 2 diabetes. No trial involving administration of low doses of selenium, on the order of 50 to 100 µg/d, has been performed so far.

An update of the meta-analysis of observational cohort studies continues to show lower risk of cancer and of some specific cancers (colorectal, prostate, and breast) in participants with highest exposure levels at baseline, but these studies are at substantial risk of bias from exposure misclassification and unmeasured confounding. In addition, results of these observational studies are inconsistent and sometimes are strongly conflicting, and no evidence of any dose-response relation emerged from our analysis

when we considered background selenium status or differences in baseline selenium exposure.

Overall, findings of our review do not provide evidence supporting a cancer–preventive effect of selenium in humans.

Implications for research

Some questions regarding selenium, such as whether selenium might influence cancer risk in individuals with very low or very high baseline exposure to this element, or in individuals with different genotypes, have not been fully resolved, although currently available evidence from randomised trials offers little support for such hypotheses. For ethical reasons, in the light of potential toxicity of selenium supplementation and failure of the most recent and well-conducted experimental cohort studies to find beneficial effects, new randomised trials on the selenium and cancer relation are unlikely to be undertaken in the future. Therefore expanding results of the SELECT trial and of other high-quality trials to examine additional outcomes such as liver cancer and non-melanoma skin cancer, as recently happened for other outcomes (Kryscio 2017; Lance 2017), and to analyse subgroups with specific characteristics (baseline selenium exposure and genetic factors), continues to appear to be the best available option for clarifying these issues. Unfortunately, most of these randomised controlled trials (RCTs), including the Selenium and Vitamin E Cancer Prevention Trial (SELECT), could not address possible sex differences because they enrolled only men.

Finally, when interpreting the results of both intervention and observational studies, it must be taken into account that various chemical forms of selenium have very different nutritional and toxicological properties, and that almost all observational studies have assessed only total selenium exposure. Future observational studies would contribute to a better understanding of the selenium and cancer relation by including selenium speciation among their exposure assessment methods when evaluating cancer risk.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agalliu 2011

Methods	Nested case-cohort study *Country:* Canada
Participants	*Name of parent cohort:* Canadian Study of Diet, Lifestyle and Health (CSDLH) *Participants:* 22,975 (alumni associations of the University of Western Ontario, 67% of 34,291) *Recruitment*: between 1995 and 1998 *Outcome assessment*: December 2003 *Number of cases:* • Prostate cancer: 661 *Case definition:* incidence *Years of follow-up:* 4.3 to 7.7 mean *Type of selenium marker:* supplementation
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age at baseline, race, BMI, exercise activity, education
Risk estimates [95% CI]	*Reference category:* zero *Results:* Prostate cancer • Highest quartile: HR 0.76 (95% CI 0.43 to 1.33)
Selenium levels in exposure categories	Lowest quartile (median value): 15.7 µg Highest quartile (median value): 105.0 µg
Notes	

Akbaraly 2005

Methods	Cohort/subcohort controlled cohort study *Country:* France
Participants	*Name of parent cohort:* Etude du Vieillissement Antériel Study (EVA study) *Participants:* 1389 (41% male, 59% female) *Inclusion criteria:* 59 to 71 years of age; residents of Nantes; able to undergo examination at study centre *Recruitment*: 1991 to 1993 *Outcome assessment*: December 2001 *Number of cases:* • Any cancer: 45 (male/female: n.r.) *Case definition:* mortality *Years of follow-up:* 9.0

Akbaraly 2005 *(Continued)*

	Type of selenium marker: plasma
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* gender, smoking, alcohol intake, medication use, obesity, diabetes mellitus, hypertension, CVD, age, education, dyslipidaemia, low cognitive function
Risk estimates [95% CI]	*Reference category:* highest quartile *Results:* Any cancer • Both genders: lowest quartile: RR 4.06 (95% CI 1.51 to 10.92)
Selenium levels in exposure categories	Lowest quartile: 14.2 to 75.0 µg/L Highest quartile: 96.3 to 155.6 µg/L
Notes	

Algotar 2013

Methods	Randomised controlled trial *Allocation:* random *Sequence generation:* unclear *Concealment:* Study agent (2 doses) and matched placebo caplets were coated with titanium oxide to ensure identical appearance, weight, taste, and smell. *Blinding:* described only as double-blinded *Dropouts/withdrawals:* Study dropout percentage was 34.1%, 41.9%, and 40.8% for placebo, 200 mg/d selenium group, and 400 mg/d selenium group, respectively (P = 0.173). *Intention-to-treat-analysis:* yes *Recruitment period:* not specified *Treatment duration:* not specified *Observation period/dermatological follow-up:* Participants were followed every 6 months for up to 5 years. *Detection of cases:* Tissue samples from participants' qualifying biopsies were requested by participants' physicians and were compiled in a biospecimen repository. *Informed consent:* An external Data and Safety Monitoring Committee (DSMC) was established before study initiation. This committee was responsible for reviewing protocol amendments, consent forms, accrual and retention rates, adverse events, and data analysis reports.
Participants	699 male participants with a negative prostate biopsy *Countries:* United States, New Zealand *Participants:* 699 (randomised to selenium 200 µg/d: 234; to selenium 400 µg/d: 233; to placebo: 233) *Condition:* male patients at high risk for prostate cancer (prostate-specific antigen (PSA) > 4 ng/mL and/or suspicious digital rectal examination and/or PSA velocity > 0.75 ng/mL/y), but with a negative prostate biopsy

Algotar 2013 *(Continued)*

	Demographics: mean age 65.2 ± SD 8 years (selenium 200 µg/d), 65.5 ± 7.7 years (selenium 400 µg/d), 65.5 ± 7.4 years (placebo) *Recruitment and setting:* urology offices at 20 sites in the United States and New Zealand
Interventions	*Intervention:* • 200 µg/d selenium supplied as selenium yeast • 400 µg/d selenium supplied as selenium yeast *Control:* placebo *Recruitment:* not reported *End of blinded treatment period:* For participants in the United States, participation was complete at 5 years, whereas those in New Zealand received intervention for no longer than 3 years.
Outcomes	*Primary outcome measure:* • Incidence of biopsy-proven prostate cancer over the course of the study *Other reported outcomes:* • Secondary endpoint was rate of change of PSA over time (i.e. PSA velocity) based on biannual PSA measurements.
Risk estimates [95% CI]	*Primary outcomes:* • Hazard ratios for risk of developing prostate cancer in the selenium 200-µg/d or the selenium 400-µg/d group were 0.94 (95% CI 0.52 to 1.7) and 0.90 (95% CI 0.48 to 1.70), respectively. *Other reported outcomes:* • PSA velocity in the selenium arms was not significantly different from that observed in the placebo group (P = 0.18 and P = 0.17, respectively).
Selenium levels in exposure categories	d.n.a.
Notes	The DSMC recommended that the trial be stopped before all participants completed the full intervention duration. *Adverse effects:* No significant differences were seen in the incidences of cataract/glaucoma or in hair/nail changes in the 3 treatment groups. *HR:* adjusted for age at baseline, baseline PSA, baseline selenium concentrations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Number-based stratified randomisation
Allocation concealment (selection bias)	Low risk	Treatments and placebo tablets of identical appearance and taste
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical appearance, weight, taste, and smell of tablets for treatments and placebo

Algotar 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	No problems found

Allen 2008

Methods	Matched, nested case-control study *Countries:* Denmark, Germany, Greece, Italy, the Netherlands, Spain, Sweden, the UK
Participants	*Participants:* approximately 130,000 men *Inclusion criteria:* male participants from the EPIC study *Name of parent cohort:* European Prospective Investigation into Cancer and Nutrition (EPIC) *Recruitment*: 1992 to 2000 *Outcome assessment*: at each country's study closure date (between June 1999 and January 2003) *Number of cases:* • Prostate cancer: 959 (male/female: 959/0) *Case definition:* incidence *Years of follow-up:* median 2.6 (Greece) to 9.2 (Sweden) *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* BMI, smoking, alcohol consumption, physical activity, marital status, education *Variables controlled by matching:* age, study centre, time of day of blood collection, time between blood collection and last meal, sex
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Prostate cancer • Highest quintile: OR 0.96 (95% CI 0.70 to 1.31)
Selenium levels in exposure categories	Lowest quintile < 62.0 µg/L Highest quintile ≥ 84.1 µg/L
Notes	

Banim 2013

Methods	Nested case-cohort study *Country:* UK
Participants	*Participants:* 23,658 men and women

Banim 2013 *(Continued)*

	Inclusion criteria: aged 40 to 74, resident in Norfolk county, registered at 35 general practices in rural, suburban, and inner city areas, no history of pancreatic cancer at enrolment or within 12 months of entering the study *Name of parent cohort:* European Prospective Investigation of Cancer-Norfolk Study (EPIC-Norfolk) *Recruitment:* 1993 to 1997 *Case definition:* incidence *Type of selenium marker:* intake Banim 2013: *Outcome assessment:* June 2010 *Number of cases:* • Pancreatic cancer: 86 (male/female: 38/48) *Years of follow-up:* 17 Barrass 2013: *Outcome assessment:* December 2010 *Number of cases:* • Renal cell carcinoma: 65 (male/female: n.r.) *Years of follow-up:* not reported (probably 17)
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, sex, smoking, diabetes, total energy intake, body mass index category, respective antioxidant supplement (only Banim 2013)
Risk estimates [95% CI]	*Reference category:* lowest quartile, lowest quintile *Results:* Banim 2013: • Pancreatic cancer: highest quartile: HR 0.72 (95% CI 0.36 to 1.43) Barrass 2013: • Renal cell cancer: highest quintile: HR 0.40 (95% CI 0.17 to 0.98)
Selenium levels in exposure categories	Banim 2013: • Lowest quartile < 43.6 µg/d • Highest quartile ≥ 72.0 µg/d Barrass 2013: • Lowest and highest quintiles not reported
Notes	

Bleys 2008

Methods	Cohort study

Bleys 2008 *(Continued)*

	Country: United States
Participants	*Name of parent cohort:* Third National Health and Nutrition Examination Survey (NHANES III) *Inclusion criteria:* male and female adults, aged 20 to 90 years, participating in the NHANES III: "stratified, multistage probability cluster to provide data representing the noninstitutionalized US population" (Bleys 2008, p. 404) *Recruitment*: 1988 to 1994 *Participants:* 13,887 men and women *Outcome assessment*: 15 December 2000 *Number of cases:* • Cancer deaths: 457 (male/female: n.r.) *Case definition:* mortality *Years of follow-up:* 6 to 12 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 457 (male/female: n.r.) *Statistical methods:* Cox proportional hazard regression *Variables controlled in analysis:* age, sex, race, education, annual family income, postmenopausal status (women), cigarette smoking, serum cotinine level, alcohol consumption
Risk estimates [95% CI]	*Reference category:* lowest tertile *Results:* Cancer deaths • Both genders: highest tertile: HR 0.69 (95% CI 0.53 to 0.90) • Both genders: highest tertile: HR 0.68 (95% CI 0.48 to 0.97); cases at baseline excluded
Selenium levels in exposure categories	Lowest tertile < 117.31 µg/L Highest tertile ≥ 130.39 µg/L
Notes	Updated results with longer follow-up for the same population reported in Goyal 2013

Brooks 2001

Methods	Matched, nested case-control study *Country:* United States
Participants	*Name of parent cohort:* Baltimore Longitudinal Study of Aging *Participants:* 1555 men *Inclusion criteria:* n.r. *Recruitment*: n.r. *Outcome assessment*: n.r. *Number of cases:* • Prostate cancer: 52 (male/female: 52/0) *Case definition:* incidence

Brooks 2001 *(Continued)*

	Years of follow-up: n.r. *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Analysed cases:* 52 of 133 (reason for non-inclusion: plasma and/or histological confirmation of diagnosis not available) *Statistical methods:* logistical regression *Variables controlled in analysis:* years between blood donation and diagnosis/follow-up, age, age by years before diagnosis interaction, BMI, smoking history, alcohol use *Variables controlled by matching:* age
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Prostate cancer • Highest quartile: OR 0.24 (95% CI 0.07 to 0.77)
Selenium levels in exposure categories	Lowest quartile: 82 to 107 µg/L Highest quartile: 133 to 182 µg/L
Notes	

Clark 1985

Methods	Cohort/subcohort controlled cohort study *Country:* United States
Participants	*Participants:* 177; no information on gender *Inclusion criteria:* persons at high risk of non-melanoma skin cancer *Recruitment*: n.r. *Outcome assessment*: n.r. *Number of cases:* • Skin (non-melanoma): 19 (male/female: n.r.) *Case definition:* incidence *Years of follow-up:* mean 3 *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard model
Risk estimates [95% CI]	*Reference category:* lower half *Results:* Skin (non-melanoma) • Sex n.r.: higher half: RR 0.77 (CI not reported)
Selenium levels in exposure categories	n.r.

Clark 1985 *(Continued)*

Notes	

Coates 1988

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 6167; both genders *Inclusion criteria:* employees of 2 Seattle companies *Recruitment*: 1972 to 1973 and 1976 *Outcome assessment*: not stated *Number of cases:* • Any cancer: 154 (male/female: n.r.) • Gastrointestinal cancer: 28 (male/female: n.r.) • Breast cancer: 20 (male/female: 0/20) • Prostate cancer: 13 (male/female: 13/0) • Haematological cancers: 12 (male/female: n.r.) • Cervical cancer: 12 (male/female: 0/12) • Lung cancer: 11 (male/female: n.r.) • Other: 58 (male/female: n.r.) *Case definition:* incidence *Years of follow-up:* n.r. *Type of selenium marker:* serum and plasma
Interventions	d.n.a.
Outcomes	*Analysed cases:* 154 (133 serum, 21 plasma) of 195 collected (reason for non-inclusion: no sample available for analysis or no control available) *Statistical methods:* conditional logistic regression *Variables controlled by matching:* age, gender, race/ethnicity, year/month of sample collection, employer, plasma or serum sample
Risk estimates [95% CI]	*Reference category:* lowest *Results:* Any cancer • Both genders: highest quintile: OR 1.0 (95% CI 0.5 to 1.8) Gastrointestinal cancer • Both genders: highest tertile: OR 1.0 (CI not reported) Breast cancer Highest tertile: OR 3.4 (CI not reported) Prostate cancer Highest tertile: OR 0.3 (CI not reported) Haematological cancers Both genders: highest tertile: OR 0.6 (CI not reported) Cervical cancer Highest tertile: OR 1.1 (CI not reported) Lung cancer Both genders: highest tertile: OR 0.8 (CI not reported) Other cancers Both genders: highest tertile: OR 0.9 (CI not reported)

Coates 1988 *(Continued)*

Selenium levels in exposure categories	*Serum:* • Lowest quintile: 98 to 142 µg/L • Highest quintile: 181 to 240 µg/L • Lowest tertile: 98 to 148 µg/L • Highest tertile: 171 to 240 µg/L *Plasma:* • Lowest quintile: 115 to 129 µg/L • Highest quintile: 157 to 207 µg/L • Lowest tertile: 115 to 137 µg/L • Highest tertile: 151 to 207 µg/L
Notes	*Primary publication:* Coates 1988 *Secondary publication:* Coates 1987

Combs 1993

Methods	Cohort/subcohort controlled cohort study *Country:* United States
Participants	*Participants:* 1239 men and women *Inclusion criteria:* participants from the NPCT with valid selenium measurement at baseline *Name of parent cohort:* Nutritional Prevention of Cancer Trial (NPCT) *Recruitment*: see: Nutritional Prevention of Cancer Trial *Outcome assessment*: not stated *Number of cases:* • Squamous cell cancer: 204 (male/female: n.r.) *Case definition:* incidence *Years of follow-up:* 2 *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, gender, current smoking, alcohol drinking
Risk estimates [95% CI]	*Reference category (unadjusted RR):* lower half *Results:* Squamous cell cancer • Both genders: higher half: unadjusted RR 0.69 (95% CI 0.51 to 0.92) • Both genders: "interquartile contrast" (high vs low), adjusted RR 0.79 (95% CI 0.67 to 0.94)
Selenium levels in exposure categories	Lower half: ≤ 114.00 µg/L Higher half: ≥ 114.10 µg/L
Notes	

Comstock 1997

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 44,960 men and women (20,305 from CLUE I; 24,655 from CLUE II) *Inclusion criteria:* residents of Washington County *Name of parent cohort:* CLUE I and II Cohort *Recruitment*: 1974/75 or 1989 *Outcome assessment*: n.r. *Number of cases:* • Lung cancer: 258 (male/female: 157/101) *Case definition:* incidence *Years of follow-up:* n.r. *Type of selenium marker:* serum/plasma
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled by matching:* age, gender, race/ethnicity, year and month of sample collection, participant of Clue I or Clue II cohort
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Lung cancer • Both genders: highest quintile: OR 0.65 (CI n.r.)
Selenium levels in exposure categories	n.r.
Notes	

Dong 2008

Methods	Cohort study *Country:* United States
Participants	*Participants:* 339 (male/female: 275/64) *Inclusion criteria:* participants from a surveillance programme for men and women with Barrett's oesophagus, no prior history of oesophageal cancer or diagnosis of cancer within first 3 months of baseline *Name of parent cohort:* Seattle Barrett's Esophagus Program *Recruitment*: 1983 to 2004, baseline assessment for this study: 1 February 1995 to 1 July 2004 *Outcome assessment:* n.r. *Number of cases:* oesophageal adenocarcinoma: 37 (male/female: 32/5) *Case definition:* incidence *Years of follow-up:* mean: 5

Dong 2008 *(Continued)*

	Type of selenium marker: intake of selenium supplements (self-administered food frequency questionnaire)
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard regression *Variables controlled in analysis:* age, sex, fruit and vegetable consumption, per cent energy from fat, waist-hip ratio, cigarette smoking, non-steroidal anti-inflammatory drug use
Risk estimates [95% CI]	*Reference category:* no supplemental selenium intake (lowest exposure category) *Results:* • Both genders: supplement intake ≥ 50 µg/d: HR 0.27 (95% CI 0.03 to 2.21)
Selenium levels in exposure categories	Lowest category: no supplemental selenium intake Middle category: supplemental selenium intake < 50 µg/d Highest category: supplemental intake ≥ 50 µg/d
Notes	

Dorgan 1998

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 6426 women *Inclusion criteria:* female volunteers with serum available at the Breast Cancer Serum Bank in Columbia (Missouri)/United States; no history of cancer at baseline; missing serum sample for analysis excluded *Recruitment*: 1987 to 1997 *Outcome assessment*: 1982 to 1983, 1989 *Number of cases:* • Breast cancer: 105 (male/female: 0/105) *Case definition:* incidence *Years of follow-up:* median: 2.7 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* serum cholesterol, packs of cigarettes/d, BMI *Variables controlled by matching:* age, year and month of sample collection, diagnosis of benign breast disease within 2 years before study enrolment, "sequence number of blood draw" for women who donate blood more than once
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Breast cancer • Highest quartile: OR 0.9 (95% CI 0.4 to 1.8)

Dorgan 1998 *(Continued)*

Selenium levels in exposure categories	Lowest quartile: ≤ 112.9 µg/L Highest quartile: 131.9 to 156.3 µg/L
Notes	

Dreno 2007

Methods	Multi-centre, randomised, placebo-controlled, parallel-group trial *Allocation:* random *Sequence generation:* unclear *Concealment:* unclear *Blinding:* described only as double-blinded *Dropouts/withdrawals:* During treatment phase, 38 in the selenium group and 37 in the placebo group withdrew from the study. This distribution was similar in both treatment groups. *Intention-to-treat-analysis:* unclear *Recruitment period:* not specified *Treatment duration:* 3 years *Observation period/dermatological follow-up:* Participants were followed for 2 years longer after treatment. *Detection of cases:* Participants were seen by a dermatologist before grafting; any participants presenting with a non-malignant or malignant skin keratosis or viral warts that had been present for less than 3 months were not selected. Within 10 weeks following the graft, a second visit was performed by a dermatologist to check that no new cutaneous lesion had appeared. *Informed consent:* The protocol and the consent form had been approved by a National Ethics Committee before the start of the study. Written informed consent was mandatory.
Participants	*Participants:* 184 (randomised to selenium 200 µg/d: 91; to placebo: 93) *Condition:* organ transplant recipient population *Demographics:* mean age 44.3 ± SD 13 years (selenium 200 µg/d), 44.4 ± 10.7 years (placebo)
Interventions	*Intervention:* • 200 µg/d selenium supplied as selenium yeast *Control:* placebo
Outcomes	*Primary outcome measure:* • Occurrence rates of warts and various keratoses *Other reported outcomes:* • Skin cancers
Risk estimates [95% CI]	*Primary outcome:* Events in selenium group = 33 (36.3%), events in placebo group = 31 (33.3%); odds ratio 1.09, P = 0.72

Dreno 2007 *(Continued)*

	Secondary outcome: Events in selenium group = 6 (6.6%), events in placebo group = 2 (2.2%); odds ratio 3.08, P = 0.15
Selenium levels in exposure categories	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multi-centre randomised
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described only as double-blinded
Selective reporting (reporting bias)	Low risk	No problems found

Epplein 2009

Methods	Matched, nested case-control study (Epplein 2009; Gill 2009) *Country:* United States
Participants	*Inclusion criteria:* participants from the Multiethnic Cohort, aged 45 to 75 years (native Hawaiians: aged 42 years and older), blood sample provided before cancer diagnosis between 1997 and 2006 *Name of parent cohort:* Multiethnic Cohort *Recruitment:* 1993 to 1996 *Case definition:* incidence *Type of selenium marker:* serum Epplein 2009: *Participants:* 67,594 (male: 29,009/female: 38,585) men and women *Outcome assessment:* 2006 *Number of cases:* • Lung cancer: 207 (male/female: 136/71) *Years of follow-up:* 0 to 10 Gill 2009: *Participants:* 29,009 men *Outcome assessment:* n.r.

Epplein 2009 *(Continued)*

	Number of cases: • Prostate cancer: 467 (male/female: 467/0) *Years of follow-up:* n.r.
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression Epplein 2009: *Variables controlled in analysis:* age, fasting hours, pack-years, pack-years squared, years of schooling, family history of lung cancer *Variables controlled by matching:* age, sex, race/ethnicity, date of sample collection, time of day of sample collection, fasting status, smoking Gill 2009: *Analysed cases:* 450 of 467 *Variables controlled in analysis:* age, fasting hours, BMI, family history of prostate cancer, education *Variables controlled by matching:* age, race/ethnicity, date of sample collection, geographic site (California, Hawaii), time of day of sample collection, fasting status
Risk estimates [95% CI]	Epplein 2009: *Reference category:* lowest tertile *Results:* Lung cancer Male: Highest tertile: OR 0.70 (95% CI 0.37 to 1.33) Female: Highest tertile: OR 0.98 (95% CI 0.42 to 2.29) Gill 2009: *Reference category:* lowest quartile *Results:* Prostate cancer Highest quartile: OR 0.82 (95% CI 0.59 to 1.14)
Selenium levels in exposure categories	Epplein 2009: Lowest tertile: median 0.12 µg/g of sodium Highest tertile: median 0.15 µg/g of sodium Gill 2009: Lowest quartile: median 0.12 µg/g Highest quartile: median 0.16 µg/g
Notes	*Primary publication:* Epplein 2009 *Other publications:* Gill 2009

Fex 1987

Methods	Matched, nested case-control study *Country:* Sweden
Participants	*Participants:* 7935 men *Inclusion criteria:* 46 to 48 years of age; residents of Malmo/Sweden; no restriction regarding malignant disease at baseline (11 of 35 with diagnosis of cancer at baseline screening examination and/or died during first year of follow-up)

Fex 1987 *(Continued)*

	Name of parent cohort: Malmo Preventive Programme *Recruitment*: 1975 to 1979 *Outcome assessment*: June 1981 *Number of cases:* • Any cancer: 35 (male/female: 35/0) *Case definition:* mortality *Years of follow-up:* 3.5 to 8.0 *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Analysed cases:* 35 of 61 (reason for non-inclusion: no plasma sample available) *Statistical methods:* logistical regression, Mantel-Haenszel *Variables controlled by matching:* age, month of sample collection
Risk estimates [95% CI]	*Reference category:* highest quintile *Results:* Any cancer Male: lowest quintiles: OR 3.8 (CI not reported)
Selenium levels in exposure categories	n.r.
Notes	CI and number of cases not reported

Fujishima 2011

Methods	Prospective cohort study *Country:* northern part of Japan
Participants	*Participants:* 1041 men and women *Inclusion criteria:* adult haemodialysis patients *Name of parent cohort:* "Kaleidoscopic Approaches to Patients with End-stage RENal Disease Study" (the KAREN Study) *Recruitment*: June 2003 to March 2004 *Number of cases:* • Malignant disease-related death: 17 *Case definition:* mortality *Years of follow-up:* 5 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox logistical regression *Variables controlled by matching:* age, male gender, BMI, hypertension, dyslipidaemia, diabetes mellitus, serum albumin levels, high-sensitivity CRP levels, history of myocardial infarction, history of stroke, history of malignant disease, smoking status, regular drinking habit

Fujishima 2011 *(Continued)*

Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Malignant disease-related death • Highest quartile: HR 2.98 (95% CI 0.62 to 14.35)
Selenium levels in exposure categories	Lowest quartile: 18.4 to 85.3 µg/L Highest quartile: 114.2 to 226.2 µg/L
Notes	

Garland 1995

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 62,641 women *Inclusion criteria:* female registered nurses in 11 USA states; aged 30 to 55 years at baseline; completed questionnaire in 1976 and provided toenail sample in 1982; no history of cancer at baseline *Name of parent cohort:* Nurses' Health Study (NHS) *Recruitment*: 1976 (toenail sample collection in 1982) *Outcome assessment*: 1 June 1986 Garland 1995: *Number of cases:* • Any cancer (without breast): 503 (male/female: 0/503) • Colon and rectal cancer: 89 (male/female: 0/89) • Melanoma: 63 (male/female: 0/63) • Ovarian cancer: 58 (male/female: 0/58) • Lung cancer: 47 (male/female: 0/47) • Other: 155 (male/female: 0/155) • Uterine cancer: 91 (male/female: 0/91) Hunter 1990: *Number of cases:* • Breast cancer: 434 (0/434) *Case definition:* incidence *Years of follow-up:* 2.0 to 4.4 *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Statistical methods:* logistical regression, conditional logistical regression *Variables controlled in analysis:* smoking status *Variables controlled by matching:* age, year and month of sample collection Hunter 1990 additionally controlled in analysis for age at first birth, age at menarche, alcohol use, history of benign breast disease, menopausal status, maternal breast cancer, breast cancer in sister(s), oral contraceptive use, parity, relative weight
Risk estimates [95% CI]	*Reference category:* lowest quintile, lowest tertile *Results:*

Garland 1995 *(Continued)*

	Garland 1995: *Any cancer (without breast)* • Female: highest quintile: OR 1.44 (95% CI 0.97 to 2.13) *Colon and rectal cancer* • Female: highest tertile: OR 2.04 (95% CI 0.88 to 4.75) *Melanoma* • Female: highest tertile: OR 1.66 (95% CI 0.71 to 3.85) *Ovarian cancer* • Female: highest tertile: OR 1.22 (95% CI 0.44 to 3.38) *Lung cancer* • Female: highest tertile: OR 4.33 (95% CI 0.54 to 34.60) *Other cancer* • Female: highest tertile: OR 0.97 (95% CI 0.55 to 1.71) *Uterine cancer* • Female: highest tertile: OR 1.38 (95% CI 0.62 to 3.08) Hunter 1990: *Breast cancer* • Female: highest quintile: OR 1.10 (95% CI 0.70 to 1.72)
Selenium levels in exposure categories	Garland 1995: • Lowest quintile: ≤ 0.71 µg/g • Highest quintile: ≥ 0.95 µg/g Hunter 1990: • Lowest quintile: ≤ 0.705 µg/g • Highest quintile: ≥ 0.906 µg/g
Notes	*Primary publication:* Garland 1995 *Other publication:* Hunter 1990

Glattre 1989

Methods	Matched, nested case-control study *Country:* Norway
Participants	*Participants:* 100,000 men and women *Inclusion criteria:* serum available at Janus serum bank (Norwegian serum bank, which is consolidated from several sources and is maintained by the Norwegian Cancer Society for research purposes) *Recruitment*: 1972 to 1985 *Outcome assessment*: end of 1985 *Number of cases:* • Thyroid cancer: 43 (male/female: 12/31) *Case definition:* incidence *Years of follow-up:* 0.0 to 14.0 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled by matching:* age, gender, year of sample collection, county of residence
Risk estimates [95% CI]	*Reference category:* highest tertile

Glattre 1989 *(Continued)*

	Results: Thyroid cancer • Both genders: lowest tertiles: OR 7.7 (95% CI 1.3 to 44.7) • Men: lowest tertiles: OR 6.5 (95% CI 0.2 to 201.9) • Women: lowest tertiles: OR 8.3 (95% CI 0.9 to 78.5)
Selenium levels in exposure categories	Lowest tertile: ≤ 98.7 µg/L Highest tertile: ≥ 130.3 µg/L
Notes	

Goodman 2001

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 18,314 (male/female: 12,025/6289) *Inclusion criteria:* 4060 male asbestos workers: 45 to 74 years of age; 14,254 (male/female: 7965/6289) smokers > 20 pack-years: 50 to 69 years of age; cohort of an RCT for lung cancer prevention in high-risk populations *Name of parent cohort:* Caret (Carotene and Retinol Efficacy Trial) *Recruitment*: 1988 to 1994 *Outcome assessment*: April 1999 *Number of cases:* • Lung cancer: 235 (male/female: n.r.) • Prostate cancer: 356 (male/female: 356/0) *Case definition:* incidence *Years of follow-up:* 6.0 to 12.0 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 235 of 236 prostate cancer cases analysed (reason for non-inclusion: no sample available for analysis or no control available); 356 of 385 lung cancer cases analysed (reason for non-inclusion: missing selenium values for case-control pairs) *Statistical methods:* conditional logistical regression *Variables controlled by matching:* age, smoking status at randomisation, year of randomisation, year of sample collection, treatment arm, exposure population
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Lung cancer • Both genders: highest quartile: OR 1.20 (95% CI 0.77 to 1.88) • Male: highest quartile: OR 1.53 (95% CI 0.83 to 2.82) • Female: highest quartile: OR 0.76 (95% CI 0.29 to 2.01) Prostate cancer • Highest quartile: OR 1.02 (95% CI 0.65 to 1.60)
Selenium levels in exposure categories	Lung cancer • Lowest quartile: 63.9 to 105.5 µg/L • Highest quartile: 129.4 to 172.3 µg/L

Goodman 2001 *(Continued)*

	Prostate cancer • Lowest quartile: 50.7 to 101.2 µg/L • Highest quartile: 126.0 to 219.6 µg/L
Notes	

Goyal 2013

Methods	Cohort study *Country:* United States
Participants	*Name of parent cohort:* Third National Health and Nutrition Examination Survey (NHANES III) *Inclusion criteria:* male and female adults, aged 20 to 90 years, participating in the NHANES III: "stratified, multistage probability cluster to provide data representing the noninstitutionalized US population" (Bleys 2008, p. 404) *Recruitment:* 1988 to 1994 *Participants:* 13,887 men and women *Outcome assessment:* 31 December 2006 *Number of cases:* • Cancer deaths: 891 (male/female: n.r.) *Case definition:* mortality *Years of follow-up:* 14.2 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 864 (male/female: n.r.) *Statistical methods:* Cox proportional hazard regression *Variables controlled in analysis:* age, sex, race-ethnicity, level of education, annual family income, body mass index, smoking status, serum cotinine level, alcohol consumption, fruit and vegetable intake, physical activity, serum total cholesterol levels, hypertension status, diabetes status, history of heart attack, congestive heart failure, stroke or cancer, hormone use in women, supplement use, serum levels of other micronutrients in the study (analysis only for both genders)
Risk estimates [95% CI]	*Reference category:* lowest tertile *Results:* Cancer deaths • Both genders: highest quintile: HR 0.84 (95% CI 0.61 to 1.17) • Male: highest quintile: HR 0.67 (95% CI 0.54 to 0.83) • Female: highest quintile: HR 0.91 (95% CI 0.71 to 1.16)
Selenium levels in exposure categories	Lowest quintile: ≤ 108.96 µg/L Highest quintile: ≥ 136.60 µg/L

Goyal 2013 *(Continued)*

Notes	Second report on the same cohort of Bleys 2008; results updated

Graff 2017

Methods	Matched, nested case-control study *Country:* United States
Participants	*Name of the parent cohort:* Health Professional Follow-up Study *Participants:* 18,259 men *Inclusion criteria:* patients free from prostate cancer between 1993 and 1995 who returned EDTA-preserved blood samples from HPFS cohort (35% of total cohort) *Recruitment:* 1986 *Outcome assessment:* 31 January 1998 *Number of cases:* • Prostate cancer: 166 (male/female: 166/0) *Case definition:* incidence *Years of follow-up:* up to 5 *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Analysesd cases:* 154 *Statistical methods:* conditional logistical regression model *Variables controlled in analysis:* age at blood draw, smoking status at blood draw, every PSA test before blood draw, timing and season of blood draw, time between blood draw and index date *Variables controlled by matching:* year of birth, PSA test before blood draw, timing, season and year of blood draw
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* • Highest quartile: 1.57 (95% CI 0.92 to 2.69)
Selenium levels in exposure categories	Lowest quartile: 0.0894 ppm Highest quartile: 0.1308 ppm
Notes	Exposure category cutpoints provided by trial author

Grundmark 2011

Methods	Cohort study

Grundmark 2011 *(Continued)*

	Country: Sweden
Participants	*Participants:* 2322 males *Inclusion criteria:* male residents in Uppsala county in January 1970, born from 1920 to 1924 *Name of parent cohort:* Uppsala Longitudinal Study of Adult Men (ULSAM) *Recruitment*: 1991 to 1995 *Outcome assessment*: 31 December 2003 *Number of cases:* • Prostate cancer: 208 *Case definition:* incidence *Years of follow-up:* median: 26.5 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* proportional hazard model
Risk estimates [95% CI]	*Reference category:* lowest level *Results:* Prostate cancer • Highest level: RR 0.83 (95% CI 0.60 to 1.16)
Selenium levels in exposure categories	Lowest level: ≤ 70 µg/L Highest level: > 81 µg/L
Notes	

Han 2013

Methods	Cohort study *Country:* United States
Participants	*Name of parent cohort:* Vitamins and Lifestyles (VITAL) study *Participants:* 70,332 men and women *Inclusion criteria:* aged 50 to 76 years, participants recruited from subscribers to commercial mailing list, residents of western Washington state, no malignant disease at baseline, no (or missing) history of pancreatic cancer or neuroendocrine tumours *Recruitment:* 1 October 2000 to 31 December 2002 *Outcome assessment:* 31 December 2008 *Number of cases:* • Pancreatic cancer: 195 (male/female: n.r.); 184 adenocarcinoma pancreatic cancer and 11 neuroendocrine tumours *Case definition:* incidence *Years of follow-up:* median: 7.1

Han 2013 *(Continued)*

	Type of selenium marker: intake and supplement use (questionnaire: use of supplements over the past 10 years, mean supplemental intake/d calculated)
Interventions	d.n.a.
Outcomes	*Analysed cases:* Individuals with neuroendocrine tumours were excluded. *Daily intake:* 162 out of 184 cases analysed (reason for exclusion: dietary questionnaire incomplete or implausible total energy intake) *Diet and 10-year supplement use:* 158 out of 184 cases analysed (reason for exclusion: dietary questionnaire incomplete or implausible total energy intake and missing supplement use) *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, sex, ethnicity, education, body mass index, physical activity, cigarette smoking status, total alcohol consumption, family history of pancreatic cancer, history of diabetes, total energy intake
Risk estimates [95% CI]	*Reference category:* lowest tertile *Results:* Adenocarcinoma pancreatic cancer • Daily intake: HR 0.44 (95% CI 0.23 to 0.85) • Diet and 10-year supplement use: HR 0.69 (95% CI 0.39 to 1.20)
Selenium levels in exposure categories	Daily intake • Lowest tertile: 6.38 to 85.49 µg/d • Highest tertile: 127.50 to 641.60 µg/d Diet and 10-year supplement use • Lowest tertile: 9.81 to 98.76 µg/d • Highest tertile: 145.66 to 646.60 µg/d
Notes	

Hansen 2013

Methods	Cohort study *Country:* Denmark
Participants	*Participants:* 54,208 men and women *Inclusion criteria:* aged 50 to 64, born in Denmark, no diagnosis of cancer registered in the Danish Cancer Registry, living in the Copenhagen, Frederiksberg Aarhus municipalities, Hinnerup or Hørning municipalities in Aarhus County, and nearly all in Copenhagen county *Recruitment:* 1993 to 1997 *Outcome assessment:* April 1995 to December 2009 *Number of cases:* 990 (male/female: n.r) *Case definition:* incidence *Years of follow-up:* median: 13 *Type of selenium marker:* supplement use
Interventions	d.n.a.

Hansen 2013 *(Continued)*

Outcomes	*Analysed cases:* • Colon-rectal cancer: 990 (male/female: n.r.) • Colon cancer: 642 (male/female: n.r.) • Rectal cancer: 348 (male/female: n.r.) *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* alcohol consumption, smoking status (ever/never), physical activity at work and at leisure, non-steroidal anti-inflammatory drug use, body mass index, education level, intake of red and processed meat, dietary intake, supplemental intake of nutrients alternatively
Risk estimates [95% CI]	*Reference category:* high use *Results:* • Colon-rectal cancer: HR 1.25 (95% CI 1.05 to 1.48) • Colon cancer: HR 1.22 (95% CI 0.99 to 1.51) • Rectal cancer: HR 1.29 (95% CI 0.96 to 1.74)
Selenium levels in exposure categories	*Supplement use:* • Never use: 0 µg/d • High use: > 45.80 µg/d
Notes	Data on dietary intake and Total intake + supplement use not reported according to inclusion criteria: only 2 categories - high vs low use

Hartman 1998

Methods	Cohort/subcohort controlled cohort study *Country:* Finland
Participants	*Participants:* 29,133 men *Inclusion criteria:* 50 to 69 years of age; smokers; no history of cancer (other than non-melanoma skin cancer) at baseline; no severe physical or psychiatric illness; intake of vitamin E/A/beta-carotene supplements in excess of defined amounts *Name of parent cohort:* Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study *Recruitment*: 1985 to 1988 *Outcome assessment*: 30 April 1993 *Number of cases:* • Prostate cancer: 302 (male/female: 302/0) *Case definition:* incidence *Years of follow-up:* 5.0 to 8.0 *Type of selenium marker:* intake
Interventions	d.n.a.
Outcomes	*Analysed cases:* 302 of 317 (reason for non-inclusion: no dietary information available) • Analysis stratified by randomisation status according to active interventions or placebo interventions in the RCT • Results reported separately for total selenium intake and non-supplemental selenium intake *Statistical methods:* Cox regression analysis *Variables controlled in analysis:* age, living in urban area, beta-carotene intervention, total energy, BPH

Hartman 1998 *(Continued)*

Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Prostate cancer *Total (nutritional and supplemental) selenium intake in participants without active alpha-tocopherol intervention* • Highest quartile: RR 1.27 (95% CI 0.70 to 2.20) *Total (nutritional and supplemental) selenium intake in participants with alpha-tocopherol intervention* • Highest quartile: RR 0.84 (95% CI 0.43 to 1.67) *Nutritional selenium intake in participants without active alpha-tocopherol intervention* • Highest quartile: RR 1.32 (95% CI 0.70 to 2.47) *Nutritional selenium intake in participants with alpha-tocopherol intervention* • Highest quartile: RR 0.72 (95% CI 0.33 to 1.55)
Selenium levels in exposure categories	Total nutritional and supplemental selenium intake: • Lowest quartile: ≤ 71.51 µg/d • Highest quartile: ≥ 111.06 µg/d Nutritional selenium intake: • Lowest quartile: ≤ 70.10 µg/d • Highest quartile: ≥ 105.65 µg/d
Notes	

Hashemian 2015

Methods	Cohort study *Country:* Iran
Participants	*Name of parent cohort:* Golestan Cohort Study *Participants:* 47,405 (male/female: 19,969/27,436) *Inclusion criteria*: aged 40 to 75, stable residents in Golestan region (Gonbad City and villages in Gonbad, Kalaleh, and Aq-Qala counties); not having a current or previous diagnosis of upper gastrointestinal cancer *Recruitment:* 2004 to 2008 *Outcome assessment:* 2014 *Number of cases:* • Oesophageal squamous cell carcinoma: 201 (male/female: n.r.) *Case definition:* incidence *Years of follow-up:* median: 7.2 *Type of selenium marker:* intake
Interventions	d.n.a.
Outcomes	*Analysed cases:* 201 (male/female: n.r.) *Statistical methods:* Cox proportional hazard model

Hashemian 2015 *(Continued)*

	Variables controlled in analysis: age, sex, total energy, place of residence (urban or rural), smoking (never or ever), wealth score (low, medium, or high), ethnicity (non-Turkmen or Turkmen), opiate use (never or ever), BMI, education (illiterate or formal education), marital status (single or married), physical activity score (continuous), fruit and vegetable intake
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Oesophageal squamous cell carcinoma • Highest quartile: HR 0.67 (95% CI 0.53 to 1.30)
Selenium levels in exposure categories	Lowest quartile: < 116 µg/d Highest quartile: > 175 µg/d
Notes	

Helzlsouer 2000

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 10,456 men *Inclusion criteria:* residents of Washington county; cases with second malignancy or missing pathological confirmation excluded *Name of parent cohort:* CLUE II Cohort *Recruitment*: 1989 *Outcome assessment*: September 1996 *Number of cases:* • Prostate cancer: 117 (male/female: 117/0) *Case definition:* incidence *Years of follow-up:* 6.8 to 7.8 *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Analysed cases:* 117 of 145 (reason for non-inclusion: no toenail clipping available) *Statistical methods:* conditional logistical regression *Variables controlled in analysis:* BMI at age 21, education, hours since last meal *Variables controlled by matching:* age, race/ethnicity, year and month of sample collection, size of toenail clipping
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Prostate cancer • Highest quintile: OR 0.38 (95% CI 0.17 to 0.85)
Selenium levels in exposure categories	Lowest quintile: ≤ 0.69 ppm Highest quintile: ≥ 0.92 ppm
Notes	

Hotaling 2011

Methods	Cohort study *Country:* United States
Participants	*Participants:* 77,050 men and women, aged 50 to 76 years, participants recruited from subscribers to commercial mailing list, residents of western Washington state, non-whites excluded, no malignant disease at baseline *Name of parent cohort:* Vitamins and Lifestyle (VITAL) study *Recruitment:* 1 October 2000 to 31 December 2002 *Outcome assessment:* 31 December 2002 *Number of cases:* • Urothelial carcinoma: 330 *Case definition:* incidence *Years of follow-up:* median: 6 *Type of selenium marker:* supplemental intake (questionnaire: use of supplements over the past 10 years, mean supplemental intake/day calculated)
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard regression *Variables controlled in analysis:* age, gender, race (white, black, other), education, family history of bladder cancer, smoking (never; former, quit more than 10 years before start of VITAL; former, quit less than 10 years before start of VITAL; current), pack-years (never-smoker and tertiles), fruit and vegetable intake
Risk estimates [95% CI]	*Reference category:* non-use *Results:* • Highest level: HR 0.97 (95% CI 0.72 to 1.31)
Selenium levels in exposure categories	Lowest level: non-use Highest quartile: 20 µg/d
Notes	

Hughes 2015

Methods	Matched, nested case-control study *Countries:* Denmark, France, Germany, Greece, Italy, the Nederlands, Spain, United Kindom
Participants	*Name of parent cohort:* European Prospective Investigation into Cancer and Nutrition (EPIC) *Participants:* 428,917 (male/female: 129,961/298,956) *Inclusion criteria:* aged 25 to 70, participants from the EPIC study *Recruitment:* 1992 to 2000 *Outcome assessment:* at each country's study closure date (between June 2002 and 2003)

Hughes 2015 *(Continued)*

	Number of cases: • Colorectal cancer: 966 (male/female: 466/500) • Colon cancer: 598 (male/female: 272/326) • Rectal cancer: 368 (male/female: 194/174) *Case definition:* incidence *Years of follow-up:* average: approximately 4 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* smoking status/duration/intensity, BMI, total physical activity, education level, total dietary energy consumption, intake of total calcium, fruits, vegetables, red and processed meats, and alcohol *Variables controlled by matching:* study centre of enrolment, sex, age at blood collection, time of blood collection and fasting status; among women, the following: menopausal status. Premenopausal women were matched on phase of menstrual cycle, and postmenopausal women were matched on current hormonal replacement therapy (HRT) use.
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Colorectal cancer • Both genders: highest quintile: IRR 0.88 (95% CI 0.64 to 1.21) • Male: highest quintile: IRR 1.18 (95% CI 0.73 to 1.90) • Female: highest quintile: IRR 0.64 (95% CI 0.40 to 1.01) Colon cancer • Both genders: highest quintile: IRR 0.81 (95% CI 0.54 to 1.23) • Male: highest quintile: IRR 1.11 (95% CI 0.58 to 2.12) • Female: highest quintile: IRR 0.61 (95% CI 0.34 to 1.09) Rectal cancer • Both genders: highest quintile: IRR 1.09 (95% CI 0.63 to 1.89) • Male: highest quintile: IRR 1.32 (95% CI 0.55 to 3.19) • Female: highest quintile: IRR 0.76 (95% CI 0.32 to 1.80)
Selenium levels in exposure categories	Both male and female • Lowest quintile: < 67.7 µg/L • Highest quintile: > 100.6 µg/L
Notes	Data for study population from Riboli 2002

Hughes 2016

Methods	Matched, nested case-control study *Countries:* Denmark, France, Germany, Greece, Italy, the Nederlands, Norway, Spain, Sweden, UK
Participants	*Name of parent cohort:* European Prospective Investigation into Cancer and Nutrition (EPIC) *Participants:* 521,448 *Inclusion criteria:* aged 25 to 70 participants of the EPIC study *Recruitment:* 1992 to 2000

Hughes 2016 *(Continued)*

	Outcome assessment: at each country's study closure date (between December 2002 and December 2006) *Number of cases:* 261 (male/female: n.r.) *Case definition:* incidence *Years of follow-up:* average: approximately 6 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* • Hepatocellular carcinoma (HCC): 106 (male/female: n.r) • Gallbladder and biliary tract cancer (GBTC): 96 (male/female: n.r) • Intrahepatic bile duct cancer (IHBC): 36 (male/female: n.r) *Statistical methods:* conditional logistical regression *Variables controlled in analysis:* BMI, waist circumference, baseline alcohol intake, physical activity (metabolic equivalent tasks), smoking status, education, alcohol intake pattern, self-reported diabetes, total energy intake *Variables controlled by matching:* age at blood collection, sex, study centre, time of day, fasting status at blood collection. Additionally, women were matched by menopausal status and hormone replacement therapy use at the time of blood collection.
Risk estimates [95% CI]	*Reference category:* lowest tertile Results • HCC: highest tertile: OR 0.41 (95% CI 0.23 to 0.72) • GBTCs: highest tertile: OR 0.74 (95% CI 0.47 to 1.18)
Selenium levels in exposure categories	Lowest tertile: ≤ 80.5 µg/L Highest tertile: ≥ 64.5 µg/L 20 µg/L increase
Notes	Estimates for IHBC reported only for 20 µg/L increase: OR 0.42 (95% CI 0.15 to 1.20)

Kabuto 1994

Methods	Matched, nested case-control study *Country:* Japan
Participants	*Participants:* 20,000 men and women *Inclusion criteria:* survivor of the atomic bomb in Hiroshima or Nagasaki; serum available for analysis *Name of parent cohort:* Adult Health Study Hiroshima and Nagasaki *Recruitment:* 1960 (blood samples drawn in 1970 to 1972) *Outcome assessment:* 1983 *Number of cases:* • Stomach cancer: 201 (male/female: 113/88) • Lung cancer: 77 (male/female: 43/34) *Case definition:* incidence *Years of follow-up:* 12.0 to 14.0

Kabuto 1994 *(Continued)*

	Type of selenium marker: serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* radiation dose, smoking, age, gender *Variables controlled by matching:* age, gender, year/month of sample collection, city
Risk estimates [95% CI]	*Reference category:* highest quartile *Results:* Stomach cancer • Both genders: lowest quartile: OR 1.0 (95% CI 0.5 to 1.9) Lung cancer • Both genders: lowest quartile: OR 1.8 (95% CI 0.7 to 5.0)
Selenium levels in exposure categories	Lowest quartile ≤ 98.90 µg/L Highest quartile ≥ 128.10 µg/L
Notes	

Karagas 1997

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 1805 men and women *Inclusion criteria:* at least 1 basal cell or squamous cell cancer before study entry; participants in an RCT for non-melanoma skin cancer prevention with oral beta-carotene supplementation *Name of parent cohort:* Skin Cancer Prevention Study *Recruitment*: February 1983 to February 1986 *Outcome assessment*: 30 September 1989 *Number of cases:* • Squamous cell cancer: 131 (89% male/11% female) *Case definition:* incidence *Years of follow-up:* 3.0 to 5.0 *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* cigarette smoking *Variables controlled by matching:* age, gender, study centre of RCT, time in study (diagnosis date)
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Squamous cell cancer Both genders: highest quartile: OR 0.86 (95% CI 0.47 to 1.58)
Selenium levels in exposure categories	Lowest quartile: ≤ 0.12 ppm Highest quartile: ≥ 0.14 ppm

Karagas 1997 *(Continued)*

Notes	

Karp 2013

Methods	Randomised controlled trial Phase III Chemoprevention Trial of Selenium Supplementation In Persons With Resected Stage I Non-Small Cell Lung Cancer: ECOG 5597 *Allocation:* random, permuted blocks stratified by smoking status (current, former, or never), sex, and stage (IA vs IB with other therapy vs IB without other therapy) *Sequence generation:* permuted blocks within strata with dynamic balancing *Concealment:* central assignments at ECOG Coordinating Center *Blinding:* participant blinded, doctor blinded, outcome assessor/pathologist unclear, review/coding of medical records unblinded *Dropouts/withdrawals:* of 1561 randomised participants, no dropouts *Intention-to-treat-analysis:* yes *Recruitment period:* 6 October 2000 to 5 November 2009 *End of study period:* 5 November 2009 *Treatment duration:* • Intervention was discontinued on 5 November 2009, following the Data Monitoring Committee recommendation that the study could eventually show significant evidence of benefit *Observation period:* After end of treatment phase, participants enter the follow-up phase. Analyses till June 2011 reported (until January 2014 in Pillai 2014 with median follow-up of 5.6 years) *Detection of cases:* visit at 3 months for adverse effects, annual visit for other endpoints *Informed consent:* yes
Participants	1561 male and female participants with completely resected stage I non-small-cell lung cancer *Countries*: United States, Canada *Participants:* 1561 (randomised to selenium group: 1,040; to placebo group: 521) *Condition:* adult participants, 6 to 36 months from complete resection of histologically proven stage IA or IB non-small-cell lung cancer, with chest X-ray or CT scan ≤ 8 weeks before registration without sign of new recurrent lung cancer, no recurrent cancers or any other prior cancer history within the past 5 years (except NMSC), normal hepatic function, ECOG performance status of 0 or 1, not taking selenium supplement regularly ≥ 70 µg/d, any therapy (chemo, radio, or biological therapy) completed at least 6 months before study registration and all related symptoms subsided *Demographics:* median age 66 in both intervention groups. Selenium and placebo participants were well balanced with respect to sex, age, smoking history, and stage at resection. *Recruitment and setting:* not reported
Interventions	*Intervention:* 200 µg selenised yeast *Control:* placebo
Outcomes	*Primary outcome:* incidence of second primary lung tumours

Karp 2013 *(Continued)*

	Secondary outcomes: incidence of any other second primary tumours, mortality, overall survival *Other outcomes:* qualitative and quantitative toxicity of selenium
Risk estimates [95% CI]	Karp 2013*:* *Primary outcome:* • Lung cancer: RR 1.23 (95% CI 0.80 to 1.80) *Other outcomes:* • Any cancer: RR 1.02 (95% CI 0.80 to 1.21) • Prostate cancer: RR 0.89 (95% CI 0.40 to 2.00) • Colorectal cancer: RR 0.50 (95% CI 0.13 to 1.91) • Melanoma: RR 1.25 (95% CI 0.24 to 6.43) • NMSC: RR 0.80 (95% CI 0.44 to 1.45) • Diabete mellitus: RR 1.19 (95% CI 0.61 to 2.35) Pillai 2014: *Primary outcome:* • Lung cancer: RR 1.29 (95% CI 0.87 to 1.93)
Selenium levels in exposure categories	d.n.a.
Notes	Karp 2013 *Adverse effects:* • Alopecia grade 1 to 2: RR 0.80 (95% CI 0.48 to 1.34) • Dermatitis grade 1 to 2: RR 1.59 (95% CI 0.75 to 3.37) • Nail changes grade 1 to 2: RR 0.72 (95% CI 0.46 to 1.12) • Fatigue grade 1 to 2: RR 1.02 (95% CI 0.68 to 1.53) • Nausea grade 1 to 2: RR 2.14 (95% CI 1.04 to 4.42)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random, permuted blocks stratified
Allocation concealment (selection bias)	Low risk	Central assignments
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants blinded and doctor blinded, outcome assessor/pathologist unclear, review/coding of medical records unblinded
Selective reporting (reporting bias)	Low risk	No problems found

Knekt 1990

Methods	Matched, nested case-control study (Hakama 1990; Knekt 1988; Knekt 1990;Knekt 1996) Cohort study (Knekt 1991) *Country:* Finland

Knekt 1990 *(Continued)*

Participants	*Inclusion criteria:* no history of cancer at baseline *Name of parent cohort:* Social Insurance Institution's Mobile Clinic Health Examination Survey *Recruitment*: 1968 to 1972 Knekt 1990: *Participants:* 39,268: 21,172 men and 18,096 women *Outcome assessment*: 31 December 1980 *Number of cases:* • Any cancer: 1096 (male/female: 597/499) • Stomach cancer: 95 (male/female: 58/37) • Colon and rectal cancer: 91 (male/female: 32/59) • Lung cancer: 198 (male/female: 189/9) • Prostate cancer: 51 (male/female: 51/0) • Urinary tract cancer: 47 (male/female: 34/13) • Pancreatic cancer: 45 (male/female: 22/23) • Breast cancer: 90 (male/female: 0/90) • Gynaecological cancer (without breast): 86 (male/female: 0/86) • Basal cell carcinoma (skin): 126 (male/female: 64/62) • Other: 267 (male/female: 147/120) Hakama 1990: *Participants:* number of participants n.r.; both genders *Inclusion criteria:* aged 15 years and older *Outcome assessment*: 1977 *Number of cases:* • Any cancer: 766 (male/female: n.r.) • Lung cancer: 151 (male/female: 151/0) • Breast cancer: 67 (male/female: 0/67) • Stomach cancer: 76 (male/female: n.r.) • Prostate cancer: 37 (male/female: 37/0) Knekt 1988: *Participants:* 36,265: 21,172 men and 15,093 women *Outcome assessment*: 31 December 1977 *Number of cases:* • Oesophageal and stomach cancer: 86 (male/female: 51/35) • Colon and rectal cancer: 57 (male/female: 21/36) Knekt 1991: *Participants:* 4538 men *Inclusion criteria:* aged 20 to 69 years, with dietary history taken *Outcome assessment*: 1986 *Number of cases:* • Lung cancer: 117 (male/female: 117/0) Knekt 1996: *Participants:* 1896 women *Outcome assessment*: 1980 *Number of cases:* • Ovarian cancer: 24 (male/female: 0/24) *Case definition:* incidence *Years of follow-up:* 9 to 20 years *Type of selenium marker:* serum (Hakama 1990; Knekt 1988; Knekt 1990;Knekt 1996), intake (Knekt 1991: dietary history)

Knekt 1990 *(Continued)*

Interventions	d.n.a.
Outcomes	Knekt 1990 *Statistical methods:* conditional logistical regression *Variables controlled in analysis:* smoking *Variables additionally controlled in analysis of highest 4 quintiles vs lowest quintile:* occupation, BMI, parity, cholesterol, haematocrit *Variables controlled by matching:* age, gender, municipality, time of baseline examination, duration of storage of sample Hakama 1990 *Analysed cases:* 766 of 864 (reason for non-inclusion: no serum sample) *Statistical methods:* conditional logistical regression *Variables controlled in analysis:* smoking *Variables additionally controlled in analysis of highest 4 quintiles vs lowest quintile:* retinol level, alpha-tocopherol level *Variables controlled by matching:* age, gender, municipality, time of baseline examination, duration of storage of sample Knekt 1988 *Statistical methods:* n.r. *Variables controlled in analysis:* smoking, serum cholesterol *Variables controlled by matching:* age, gender, municipality, time of baseline examination, duration of storage of sample Knekt 1991 *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, smoking (data stratified according to smoking status) Knekt 1996 *Statistical methods:* conditional logistical regression *Variables controlled by matching:* age, gender, municipality, time of baseline examination, duration of storage of sample
Risk estimates [95% CI]	Knekt 1990 *Reference category:* lowest quintile *Results:* *Any cancer* Male • Highest quintile: OR 0.41 (CI not reported) • Above 20th percentile: OR 0.67 (CI not reported); cases during first 2 years of follow-up excluded: 476 cases: OR 0.65 (95% CI 0.48 to 0.89) Female • Highest quintile: OR 0.86 (CI not reported) • Above 20th percentile: OR 0.93 (CI not reported); cases during first 2 years of follow-up excluded: 423 cases: OR 0.97 (95% CI 0.68 to 1.39) *Stomach cancer* Male • Highest quintile: OR 0.09 (CI not reported) • Above 20th percentile: OR 0.26 (CI not reported); cases during first 2 years of follow-up excluded: 43 cases: OR 0.24 (95% CI 0.09 to 0.69) Female • Highest quintile: OR 0.27 (CI not reported) • Above 20th percentile: OR 0.59 (CI not reported); cases during first 2 years of follow-up excluded: 30 cases: OR 0.48 (95% CI 0.14 to 1.66) *Colon and rectal cancer* Male • Highest quintile: OR 0.53 (CI not reported) • Above 20th percentile: OR 0.69 (CI not reported); cases during first 2 years of follow-up excluded: 29 cases: OR 1.01 (95% CI 0.18 to 5.65)

Knekt 1990 *(Continued)*

Female
• Highest quintile: OR 0.80 (CI not reported)
• Above 20th percentile: OR 1.26 (CI not reported); cases during first 2 years of follow-up excluded: 48 cases: OR 1.10 (95% CI 0.42 to 2.92)
Lung cancer
Male
• Highest quintile: OR 0.30 (CI not reported)
• Above 20th percentile: OR 0.60 (CI not reported); cases during first 2 years of follow-up excluded: 153 cases: OR 0.66 (95% CI 0.37 to 1.19)
Female
• Third highest quintile: OR 4.62 (CI not reported) (quintile 4 and 5 did not contain any cases)
Prostate cancer
• Highest quintile: OR 1.15 (CI not reported)
• Above 20th percentile: OR 1.13 (CI not reported); cases during first 2 years of follow-up excluded: 46 cases: OR 1.00 (95% CI 0.42 to 2.40)
Urinary tract cancer
Male
• Highest quintile: OR 0.81 (CI not reported)
• Above 20th percentile: OR 0.89 (CI not reported); cases during first 2 years of follow-up excluded: 26 cases: OR 0.34 (95% CI 0.06 to 2.06)
Female
• Highest quintile: OR 4.12 (CI not reported)
• Above 20th percentile: not reported; cases during first 2 years of follow-up excluded: 9 cases: OR 2.51 (95% CI 0.13 to 47.9)
Pancreatic cancer
Male
• Fourth quintile vs lowest: OR 0.58 (CI not reported) (highest quintile did not contain any cases)
• Above 20th percentile: OR 0.11 (CI not reported); cases during first 2 years of follow-up excluded: not reported
Female
• Highest quintile: OR 3.49 (CI not reported)
• Above 20th percentile: not reported; cases during first 2 years of follow-up excluded: 22 cases: OR 0.86 (95% CI 0.21 to 3.52)
Breast cancer
• Highest quintile: OR 0.64 (CI not reported)
• Above 20th percentile: OR 0.52 (CI not reported); cases during first 2 years of follow-up excluded: 74 cases: OR 0.57 (95% CI 0.18 to 1.81)
Gynaecological cancer (without breast)
• Highest quintile: OR 0.96 (CI not reported)
• Above 20th percentile: OR 0.91 (CI not reported); cases during first 2 years of follow-up excluded: 70 cases: OR 1.03 (95% CI 0.43 to 2.50)
Basal cell carcinoma (skin)
Male
• Highest quintile: OR 0.54 (CI not reported)
• Above 20th percentile: OR 0.65 (CI not reported); cases during first 2 years of follow-up excluded: 54 cases: OR 0.86 (95% CI 0.35 to 2.12)
Female
• Highest quintile: OR 1.55 (CI not reported)
• Above 20th percentile: OR 1.73 (CI not reported); cases during first 2 years of follow-up excluded: 52 cases: OR 1.54 (95% CI 0.64 to 3.73)
Other or unspecified cancer:
Male
• Highest quintile: OR 0.42 (CI not reported)
• Above 20th percentile: OR 0.72 (CI not reported); cases during first 2 years of follow-up excluded: 110 cases: OR 0.70 (95% CI 0.36 to 1.36)
Female
• Highest quintile: OR 0.71 (CI not reported)
• Above 20th percentile: OR 0.87 (CI not reported); cases during first 2 years of follow-up excluded: 111 cases: OR 0.92 (95% CI 0.44 to 1.92)

Hakama 1990

Knekt 1990 *(Continued)*

Reference category: highest quintile

Results:
Any cancer
Male
• Lowest quintile: OR 2.40 (CI not reported)
• Lowest quintile vs 4 highest quintiles: OR 1.60 (CI not reported)
Female
• Lowest quintile: OR 1.20 (CI not reported)
• Lowest quintile vs 4 highest quintiles:0.90 (CI not reported)
Lung cancer
Male:
• Lowest quintile vs 4 highest quintiles: OR 1.80 (CI not reported)
Breast cancer
• Lowest quintile vs 4 highest quintiles: OR 3.10 (CI not reported)
Stomach cancer
Male
• Lowest quintile vs 4 highest quintiles: OR 6.70 (CI not reported)
Female
• Lowest quintile vs 4 highest quintiles: OR 2.00 (CI not reported)
Prostate cancer
• Lowest quintile vs 4 highest quintiles: OR 0.80 (CI not reported)

Knekt 1988
Reference category: highest quintile

Results:
Oesophageal and stomach cancer
Male
• Lowest tertile: OR 2.20 (CI not reported)
• Lowest quintile vs 4 highest quintiles: OR 3.3 (95% CI 1.3 to 9.1)
Female
• Lowest tertile: OR 1.50 (CI not reported)
• Lowest quintile vs 4 highest quintiles: OR 2.4 (95% CI 0.7 to 8.3)
Colon and rectal cancer
Male
• Lowest tertile: OR 0.90 (CI not reported)
• Lowest quintile vs 4 highest quintiles: OR 1.7 (95% CI 0.4 to 7.7)
Female
• Lowest tertile: OR 0.60 (CI not reported)
• Lowest quintile vs 4 highest quintiles: OR 0.8 (95% CI 0.2 to 2.4)

Knekt 1991
Reference category: highest tertile

Results:
Lung cancer
Male non-smokers

• Lowest tertile: OR 1.03 (CI not reported)
Male smokers

• Lowest tertile: OR 0.83 (CI not reported)

Knekt 1996
Reference category: highest tertile

Results:
Ovarian cancer
• Lowest tertile: OR 1.15 (95% CI 0.19 to 4.06)

Knekt 1990 *(Continued)*

Selenium levels in exposure categories	Knekt 1990 • Lowest quintile: ≤ 48.90 µg/L • Highest quintile ≥ 78.00 µg/L Hakama 1990 • Quintiles: not specified Knekt 1988 *Both genders* • Lowest tertile: ≤ 56.90 µg/L • Highest tertile ≥ 70.10 µg/L • Lowest quintile: ≤ 50 µg/L • Highest 4 quintiles > 50 µg/L Knekt 1991 • Tertiles: n.r. Knekt 1996 • Lowest tertile: ≤ 56.90 µg/L • Highest tertile: ≥ 68.10 µg/L
Notes	*Primary publication:* Knekt 1990 *Other publications:* Hakama 1990, Knekt 1988, Knekt 1991, Knekt 1996

Knekt 1998

Methods	Matched, nested case-control study *Country:* Finland
Participants	*Participants:* 9101 men and women *Inclusion criteria:* 19 years or older; no history of cancer at baseline; serum sample available for analysis *Name of parent cohort:* Social Insurance Institution's Mobile Clinic Health Examination Survey *Recruitment*: 1973 to 1976 *Outcome assessment*: end of 1991 *Number of cases:* • Lung cancer: 91 (male/female: approximately 95%/5%) *Case definition:* incidence *Years of follow-up:* 16.0 to 19.0 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 91 of 95 (male/female: 90/5) *Statistical methods:* conditional logistical regression *Variables controlled in analysis:* smoking, alpha-tocopherol, serum cholesterol, copper, orosomucoid, BMI *Variables controlled by matching:* age, gender, municipality, season of sample collection, length of storage of sample
Risk estimates [95% CI]	*Reference category:* lowest tertile

Knekt 1998 *(Continued)*

	Results: Lung cancer • Analysis adjusted for smoking only: both genders: highest tertiles: OR 0.44 (95% CI 0.21 to 0.89) • Analysis adjusted for all variables (number of cases: 77): highest tertiles: OR 0.41 (95% CI 0.17 to 0.94)
Selenium levels in exposure categories	Lowest tertile: ≤ 45.49 µg/L Highest tertile: ≥ 60.60 µg/L
Notes	

Kok 1987a

Methods	Matched, nested case-control study *Country:* the Netherlands
Participants	*Participants:* 10,532 men and women *Inclusion criteria:* inhabitant of Zoetermeer; 5 years or older *Name of parent cohort:* EPOZ Cohort (Epidemiologisch onderzoek naar risico-indicatoren voor hart- en vaatziekten) *Recruitment*: 1975 to 1978 *Outcome assessment*: 31 December 1983 *Number of cases:* • Any cancer: 69 (male/female: 40/29) *Case definition:* mortality *Years of follow-up:* 6.0 to 9.0 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 69 of 114 (reason for non-inclusion: serum or baseline data not available, deaths in first year of follow-up excluded) *Statistical methods:* not specified *Variables controlled in analysis:* age, smoking, serum cholesterol, serum vitamins A and E, systolic and diastolic blood pressure, BMI, week of blood collection, years of education, gender (in group of both genders) *Variables controlled by matching:* age, gender, smoking status
Risk estimates [95% CI]	*Reference category:* highest 4 quintiles *Results:* *Any cancer* • Both genders: lowest quintile: OR 1.9 (90% CI 1.0 to 3.5) • Male: lowest quintile: OR 2.7 (90% CI 1.2 to 6.2) • Female: lowest quintile: OR 1.5 (90% CI 0.5 to 4.5)
Selenium levels in exposure categories	Both genders • Lowest quintile: ≤ 102.79 µg/L • Highest 4 quintiles: ≥ 102.80 µg/L Males • Lowest quintile: ≤ 100.79 µg/L • Highest 4 quintiles: ≥ 100.80 µg/L

Kok 1987a *(Continued)*

	Females • Lowest quintile: ≤ 107.29 µg/L • Highest 4 quintiles: ≥ 107.30 µg/L
Notes	*Primary publication:* Kok 1987b *Other publication:* Kok 1987a

Kornitzer 2004

Methods	Matched, nested case-control study *Country:* Belgium
Participants	*Participants:* 10,902 (male/female: 5,549/5,353) *Inclusion criteria:* 25 to 74 years of age *Name of parent cohort:* Belgian Interuniversity Study on Nutrition and Health *Recruitment*: 1980 to 1984 *Outcome assessment:* n.r. *Number of cases:* • Any cancer: 193 (male/female: 143/50) *Case definition:* mortality *Years of follow-up:* 10 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 143 male/50 female cases analysed from 252 male/91 female cases (reason for non-inclusion: no selenium measurement available) *Statistical methods:* not specified *Variables controlled in analysis:* BMI, total energy, total fat, saturated fat, alcohol intake, fibre, retinol, vitamin C, smoking, beta-carotene *Variables controlled by matching:* age, gender
Risk estimates [95% CI]	*Reference category:* highest tertile *Results:* Any cancer • Male: lowest tertile: OR 2.2 (95% CI 1.3 to 3.7) • Female: lowest tertile: OR 0.7 (95% CI 0.3 to 1.6)
Selenium levels in exposure categories	Lowest tertile ≤ 72.00 µg/L Highest tertile ≥ 85.00 µg/L
Notes	

Kristal 2014

Methods	Matched, nested case-control study *Countries:* United States, Canada, Puerto Rico

Kristal 2014 *(Continued)*

Participants	*Name of parent cohort:* SELECT (Selenium and Vitamin E Cancer Prevention Trial), placebo arm *Participants:* 777 men from placebo arm of SELECT study *Inclusion criteria:* black men aged ≥ 50 years and all other men aged ≥ 55 years, without history of prostate cancer, serum PSA level ≤ 4 ng/L and non-suspicious digital rectal examination *Recruitment:* July 2001 to May 2004 *Outcome assessment:* 31 July 2009 *Number of cases:* • Prostate cancer: 404 (male/female:404/0) *Case definition:* incidence *Years of follow-up*: n.r. *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Analysed cases:* 404 (male/female: 404/0) *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age and race by matching, family history of prostate cancer, diabetes, body mass index, prostate-specific antigen *Variables controlled by matching:* age and race
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* • Prostate cancer: highest quintile: HR 0.76 (95% CI 0.44 to 1.31)
Selenium levels in exposure categories	Lowest quintile: < 0.758 µg/g Highest quintile > 1.003 µg/g
Notes	

Kromhout 1987

Methods	Cohort/subcohort controlled cohort study *Country:* the Netherlands
Participants	*Participants:* 878 men *Inclusion criteria:* 40 to 59 years of age; random sample of general male population at specific age in Zutphen *Name of parent cohort:* Zutphen Study *Recruitment*: 1960 *Outcome assessment*: 1985 *Number of cases:* • Lung cancer: 63 (male/female: 63/0) *Case definition:* mortality

Kromhout 1987 *(Continued)*

	Years of follow-up: 25 *Type of selenium marker:* intake (interview)
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, pack-years of smoking
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Lung cancer • Male: highest quartile: RR 0.98 (95% CI 0.41 to 2.36)
Selenium levels in exposure categories	Lowest quartile: ≤ 55.00 µg/d Highest quartile: ≥ 72.10 µg/d
Notes	

Li 2000

Methods	Randomised controlled trial *Allocation:* randomised, "based on their residence area" *Sequence generation:* unclear, not described *Concealment:* unclear, not described *Blinding: of participants:* adequate (placebo); *of investigators and doctors:* unclear, not described *Dropouts/withdrawals:* no significant difference between percentages of dropouts in intervention and control group (absolute numbers not reported) *Intention-to-treat-analysis:* unclear *Recruitment period:* unclear, not described *Observation period:* 3 years, started in 1996 *Study period:* unclear, not described *Detection of cases:* unclear; the study followed the diagnostic menu published by the National Cancer Control and Prevention Center, follow-up procedures not described *Informed consent:* unclear, not described
Participants	*Country:* China *Number of participants:* 2065 (selenium group: 1112; placebo group: 953) *Condition:* HBs-Ag carriers with negative AFP and normal ALT living in Qidong, Jiangsu province *Demographics:* men only; aged 20 to 65 years (screening group) *Recruitment and setting:* recruitment of 2065 HBs-Ag carriers from 17 villages out of a screening group of 18,000 men
Interventions	*Intervention:* 0.5 mg sodium selenite p.o. daily for 3 years

Li 2000 *(Continued)*

	Control: placebo
Outcomes	*Primary outcome measure:* incidence of primary liver cancer *Other:* blood selenium levels, activity of glutathione peroxidase *Results:* person-year incidence rate (number of cases/total number of persons) in intervention and control groups: • 1st year of follow-up: selenium group 899.25/100,000 (10/1112); placebo group: 1888.77/100,000 (18/953) • 2nd year of follow-up: selenium group 1708.60/100,000 (19/1112); placebo group: 4302.20/100,000 (41/953) • 3rd year of follow-up: selenium group 3057.55/100,000 (34/1112); placebo group: 5981.11/100,000 (57/953)
Risk estimates [95% CI]	n.r.
Selenium levels in exposure categories	d.n.a.
Notes	Adverse effects were not mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation based only on residential area
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and doctors
Selective reporting (reporting bias)	Low risk	No problems found

Li 2004a

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 14,916 men *Inclusion criteria:* participants of Physicians' Health Study who provided blood sample (healthy male physicians); no history of cancer at baseline; several physical conditions excluded at baseline: chronic renal failure, unstable angina pectoris, liver disease, peptic ulcer, history of TIA/stroke/myocardial infarction/gout; no use of vitamin A or beta-carotene supplements *Name of parent cohort:* Physicians' Health Study *Recruitment*: 1982 *Outcome assessment*: 1995

Li 2004a *(Continued)*

	Number of cases: • Prostate cancer: 586 (male/female: 586/0) *Case definition:* incidence *Years of follow-up:* 13 *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Statistical methods:* logistical regression *Variables controlled in analysis:* age at baseline, smoking status, duration of follow-up *Variables controlled by matching:* age, smoking status
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Prostate cancer • Highest quintile: OR 0.78 (95% CI 0.54 to 1.13)
Selenium levels in exposure categories	Lowest quintile: 0.060 to 0.090 ppm Highest quintile: 0.121 to 0.190 ppm
Notes	

Lubinski 2011

Methods	Randomised controlled trial *Allocation:* random *Sequence generation:* unclear *Concealment:* unclear *Blinding:* described only as double-blinded *Dropouts/withdrawals:* no description *Intention-to-treat-analysis:* unclear *Recruitment period:* not specified *Treatment duration:* unclear *Observation period/dermatological follow-up:* • Median: 35 months (range 6 to 62 months) *Detection of cases:* not described *Informed consent:* not described
Participants	*Country:* Poland *Number of participants:* 1135 (randomised to selenium group: 563, to placebo group: 572) *Condition:* adult women, *BRCA1*+ mutation carriers *Demographics:* not reported

Lubinski 2011 *(Continued)*

	Recruitment and setting: not reported
Interventions	*Intervention:* • 250 µg/d selenium supplied as sodium selenite *Control:* • Placebo
Outcomes	*Case definition:* incidence • All cancer • Primary breast cancer • Ovarian cancer
Risk estimates [95% CI]	All cancer: HR 1.4 (95% CI 0.9 to 2.0), cases: selenium 60, placebo 45 Primary breast cancer: HR 1.3 (95% CI 0.7 to 2.5), cases: selenium 38, placebo 29 Ovarian cancer: HR 1.3 (95% CI 0.6 to 2.7), cases: selenium 17, placebo 10
Selenium levels in exposure categories	d.n.a
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described only as randomised trial
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described only as double-blinded
Selective reporting (reporting bias)	Low risk	No problems found

Ma 2017

Methods	Cohort study *Country:* China
Participants	Name of parent cohorts: Shangai Men's Health Study (SMHS) and Shangai Women's Health Study (SWHS) *Participants:* 133,957 (male/female: 61,470/74,941) SMHS: 61,480 men SWHS: 74,941 women

Ma 2017 *(Continued)*

	Inclusion criteria: SMHS: men aged 40 to 74; residents in Shangai with no history of cancer SWHS: women aged 40 to 70, residents in Shangai with no history of cancer *Recruitment:* SMHS: April 2002 to June 2006 SWHS: March 1997 to May 2000 Outcome assessment: 31 December 2012 Number of cases: 536 (male/female: 344/192) *Case definition:* incidence *Years of follow-up:* SMHS: median: 9.3 SWHS: median: 15.2 *Type of selenium marker:* intake
Interventions	d.n.a.
Outcomes	*Analysed cases:* • Hepatocellular carcinoma: 536 (male/female: 344/192) *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* • Both genders: sex, age at recruitment, body mass index, total physical activity, total intake of energy, vegetable, fruit, red meat, egg, fish, and soy, vitamin E intake, income, education, smoking history, alcohol consumption, family history of liver cancer, history of viral hepatitis/chronic liver disease, history of diabetes, history of cholelithiasis and history of cholecystectomy • Men: age at recruitment, body mass index, total physical activity, total intake of energy, vegetable, fruit, red meat, egg, fish, and soy, vitamin E intake, income, education, smoking history, alcohol consumption, family history of liver cancer, history of viral hepatitis/chronic liver disease, history of diabetes, history of cholelithiasis and history of cholecystectomy • Women: age at recruitment, body mass index, total physical activity, total intake of energy, vegetable, fruit, red meat, egg, fish, and soy, vitamin E intake, income, education, smoking history, alcohol consumption, family history of liver cancer, history of viral hepatitis/chronic liver disease, history of diabetes, history of cholelithiasis, history of cholecystectomy, menopausal status, ever had oral contraceptive
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Hepatocellular carcinoma • Both cohorts: highest quintile: HR 0.86 (95% CI 0.52 to 1.43) SMHS: highest quintile: HR 0.95 (95% CI 0.51 to 1.76) SWHS: highest quintile: HR 0.70 (95% CI 0.26 to 1.90)
Selenium levels in exposure categories	SMHS: • Lowest quintile: < 31.77 µg/d • Highest quintile: ≥ 54.52 µg/d SWHS: • Lowest quintile: < 36.24 µg/d • Highest quintile: ≥ 61.14 µg/d
Notes	

Marshall 2011

Methods	Randomised controlled trial *Allocation:* random *Sequence generation: unclear* *Concealment:* unclear *Blinding:* described only as double-blinded. The central pathologist was also blinded to study assignment. *Dropouts/withdrawals:* 13/227 in the selenium arm and 12/225 in the placebo arm were lost to follow-up. *Intention-to-treat-analysis:* yes *Recruitment period:* not specified *Treatment duration:* not specified *Observation period/dermatological follow-up:* • Participants were followed for 3 years. They were seen in clinic at baseline and every 6 months thereafter. *Detection of cases:* Tissue blocks and corresponding pathology reports for all prostate procedures were to be submitted to the central study pathologist for review. *Informed consent:* All participants gave oral and written informed consent in accordance with institutional and federal guidelines. The protocol was approved by the Institutional Review Boards at participating institutions, and was monitored by the Data and Safety Monitoring Committee of SWOG.
Participants	*Country:* United States *Participants:* 452 (randomised to selenium 200 µg/d: 227; to placebo group: 225) *Condition:* 40 years of age or older; digital rectal examination; biopsy-confirmed diagnosis of HGPIN with no evidence of cancer; upper limit of prostate-specific antigen (PSA) of 10 ng/mL (as measured locally); American Urological Association (AUA) symptom score < 20 (41), signifying no debilitating urinary problems; ambulatory and able to carry out work of a light or sedentary nature *Demographics:* Selenium and placebo participants were well balanced with respect to age, race, ethnicity, pre-study PSA category, vitamin E supplements, and number of cores in the initial biopsy. They also were well balanced in body mass index, baseline blood selenium, performance status, and number of cores revealing HGPIN.
Interventions	Participants were randomised in fashion to placebo or 200 µg/d of selenium, with daily treatment scheduled for 3 years or until a prostate cancer diagnosis. *Recruitment:* not reported *End of blinded treatment period:* at 3 years
Outcomes	*Primary outcome measure:* • progression of HGPIN to prostate cancer over a 3-year period
Risk estimates [95% CI]	*Primary outcomes:* • Adjusted OR 0.913 (95% CI 0.55 to 1.52, P = 0.727) for risk of prostate cancer as a function of treatment group (with placebo as referent group)

Marshall 2011 *(Continued)*

Selenium levels in exposure categories	d.n.a.
Notes	OR estimate was given by the trial author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised
Allocation concealment (selection bias)	Low risk	Central randomisation with pathology review
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and personnel
Selective reporting (reporting bias)	Low risk	No problems found

McNaughton 2005

Methods	Matched, nested case-control study (McNaughton 2005b) Cohort study (Heinen 2007; van der Pols 2009) *Country:* Australia
Participants	*Name of parent cohort:* Nambour Skin Cancer Study *Recruitment:* 1992 to 1996 *Case definition:* incidence McNaughton 2005b *Participants:* approximately 1000 men and women *Inclusion criteria:* randomly selected adults, aged 20 to 69 years; recruited for participation in a randomised controlled trial for skin cancer prevention with beta-carotene supplements and sunscreen application in 1992; living in the Nambour community; free of SCC at baseline; blood sample and FFQ provided in 1996; participants with extreme energy intakes in FFQ excluded *Outcome assessment:* December 2001 *Number of cases:* • Basal cell carcinoma of the skin: 90 (male/female: 39/51) *Years of follow-up:* 5.5 *Type of selenium marker:* serum and intake (FFQ) Heinen 2007 *Participants:* 1001 men and women *Inclusion criteria:* randomly selected adults, aged 20 to 69 years; recruited for participation in randomised controlled trial for skin cancer prevention with beta-carotene supplements and sunscreen application in 1992; living in the Nambour community; blood sample and FFQ provided in 1996; partici-

McNaughton 2005 *(Continued)*

	pants with extreme energy intakes in FFQ and missing consumption frequencies for more than 10% of food items excluded *Outcome assessment*: 31 December 2004 *Number of cases:* • Basal cell carcinoma of the skin: 149 (male/female: 87/62) participants with 321 BCC tumours • Squamous cell carcinoma of the skin: 116 (male/female: 70/46) participants with 221 SCC tumours *Case definition:* incidence (tumour-based incidence and person-based incidence) *Years of follow-up:* 8 *Type of selenium marker:* intake (FFQ) van der Pols 2009: *Participants:* 485 (male/female: 223/262) men and women *Inclusion criteria:* randomly selected adults, aged 20 to 69 years; recruited for participation in randomised controlled trial for skin cancer prevention with beta-carotene supplements and sunscreen application in 1992; randomised to placebo in the intervention trial; living in the Nambour community; free of SCC at baseline; blood sample and FFQ provided in 1996; participants with extreme energy intakes in FFQ excluded *Outcome assessment:* 31 December 2004 *Number of cases:* • Basal cell carcinoma of the skin: 77 (male/female: 46/31) participants with 173 BCC tumours • Squamous cell carcinoma of the skin: 59 (male/female: 38/21) participants with 124 SCC tumours *Years of follow-up:* 8 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	McNaughton 2005b: *Statistical methods:* conditional logistical regression *Variables controlled in analysis:* age, gender *Variables controlled by matching:* age, gender Heinen 2007 *Statistical methods:* generalised linear models *Variables controlled in analysis:* age, sex, intervention arm in RCT, energy intake, skin colour, elastosis of the neck, smoking, use of dietary supplements, history of skin cancer van der Pols 2009 *Statistical methods:* generalised linear models *Variables controlled in analysis:* age, sex, pack-years of smoking, alcohol intake, time spent outdoors on weekdays, history of skin cancer before 1996
Risk estimates [95% CI]	McNaughton 2005b *Reference category:* lowest quartile *Results:* Basal cell carcinoma (skin) • Both genders: highest quartile: OR 0.86 (95% CI 0.38 to 1.96) biochemical selenium level • Both genders: highest quartile: OR 1.13 (95% CI 0.47 to 2.74) selenium intake Heinen 2007 *Reference category:* lowest tertile

McNaughton 2005 *(Continued)*

	Results: Basal cell carcinoma (skin) • Both genders: highest tertile: RR 0.95 (95% CI 0.59 to 1.50) Squamous cell carcinoma (skin) • Both genders: highest tertile: RR 1.3 (95% CI 0.77 to 2.3) van der Pols 2009 *Reference category:* lowest exposure category *Results:* Basal cell carcinoma (skin) • Both genders: highest exposure category: RR 0.58 (95% CI 0.32 to 1.07) Squamous cell carcinoma (skin) • Both genders: highest exposure category: RR 0.49 (95% CI 0.24 to 0.99)
Selenium levels in exposure categories	McNaughton 2005b n.r. Heinen 2007 • Lowest tertile ≤ 76.20 µg/d • Highest tertile ≥ 89.31 µg/d van der Pols 2009 • Lowest exposure category ≤ 78.96 µg/L • Highest exposure category ≥ 102.65 µg/L
Notes	*Primary publication:* McNaughton 2005b *Other publications:* Heinen 2007, van der Pols 2009 Tumour-based incidence: number of newly developed histologically confirmed BCCs or SCCs divided by person-years of follow-up accumulated over follow-up period Person-based incidence: number of persons newly affected by BCC or SCC during the same person-years of follow-up time as calculated for the tumour-based analysis

Menkes 1986

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 20,305 men and women *Inclusion criteria:* female and male inhabitants of Washington county/Maryland; history of cancer at baseline excluded *Name of parent cohort:* CLUE I Cohort *Recruitment*: September to November 1974 Menkes 1986b *Outcome assessment*: 1983 *Number of cases:* • Lung cancer: 99 (69% male/31% female) Helzlsour 1996 *Inclusion criteria:* women only; women who used hormones at baseline excluded *Outcome assessment*: 1989 *Number of cases:* • Ovarian cancer: 35 (male/female: 0/35)

Menkes 1986 *(Continued)*

	Breslow 1995 *Outcome assessment*: 1994 *Number of cases:* • Melanoma: 23 (male/female: n.r.) • Basal cell carcinoma (skin): 17 (male/female: n.r.) • Squamous cell cancer: 37 (male/female: n.r.) Zheng 1993 *Outcome assessment*: 1990 *Number of cases:* • Oral and pharyngeal: 28 (male/female: n.r.) Batieha 1993 *Inclusion criteria:* 15,161 women *Outcome assessment*: 31 May 1990 *Number of cases:* • Cervical cancer: 50 (male/female: 0/50) Helzlsour 1989 *Inclusion criteria:* 20,305 men and women *Outcome assessment*: 1986 *Number of cases:* • Bladder cancer: 35 (male/female: n.r.) Burney 1989 *Outcome assessment*: 1986 *Number of cases:* • Pancreatic cancer: 22 (male/female: 9/13) Ko 1994 *Outcome assessment*: 25 September 1991 *Number of cases:* • Colon cancer: 121 (male/female: 50/71) *Case definition:* incidence *Years of follow-up:* 8.0 to 16.8 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	Menkes 1986b *Statistical methods:* conditional logistical regression *Variables controlled by matching:* age, gender, race/ethnicity, smoking status, year and month of sample collection Helzlsour 1986 *Statistical methods:* conditional logistical regression *Variables controlled by matching:* age, race/ethnicity, day and time of blood sample collection, hours since last meal, time since last menstrual period (postmenopausal: years, premenopausal: days) Breslow 1995 *Statistical methods:* conditional logistical regression *Analysed cases:* 17 of 98 basal cell carcinoma cases and 23 of 30 melanoma cases (and all squamous cell carcinoma cases) included in analysis *Variables controlled by matching:* age, gender, race/ethnicity

Menkes 1986 *(Continued)*

Zheng 1993
Statistical methods: n.r.
Variables controlled in analysis: smoking
Variables controlled by matching: age, gender, race/ethnicity, year and month of sample collection, hours between previous meal and blood collection

Batieha 1993
Statistical methods: conditional logistical regression
Analysed cases: 50 of 60 (CIS and invasive cervical cancer) (reason for non-inclusion: no matched control available)
Variables controlled by matching: age, race/ethnicity, year and month of blood collection, hours since last meal, time since last menstrual period

Helzlsour 1989
Statistical methods: n.r.
Variables controlled in analysis: cigarette smoking, use of vitamin supplements
Variables controlled by matching: age, gender, race/ethnicity, hours since last meal (all samples collected in same year)

Burney 1989
Statistical methods: n.r.
Variables controlled by matching: age, gender, race/ethnicity, hours since last meal

Ko 1994
Analysed cases: 121 of 154 (reason for non-inclusion: no serum sample available, tumour pathology or localisation unclear)
Statistical methods: conditional logistical regression
Variables controlled by matching: age, gender, race/ethnicity, year and month of sample collection, hours since last meal, women: time since last menstrual period, women: use of hormones/hormonal contraceptives

Risk estimates [95% CI]

Menkes 1986b
Reference category: highest quintile

Results:
Lung cancer
• Both genders: lowest quintile: OR 0.68 (CI not reported)

Helzlsouer 1986
Reference category: lowest tertile

Results:
Ovarian cancer
• Highest tertiles: OR 0.58 (95% CI 0.20 to 1.70)

Breslow 1995
Reference category: lowest tertile

Results:
Melanoma
• Both genders: highest tertile: OR 0.9 (95% CI 0.3 to 2.5)
Basal cell carcinoma (skin)
• Both genders: highest tertile: OR 0.8 (95% CI 0.1 to 4.5)
Squamous cell cancer
• Both genders: highest tertile: OR 0.6 (95% CI 0.2 to 1.5)

Zheng 1993
Reference category: lowest tertile

Results:
Oral and pharyngeal cancer
• Both genders: highest tertile: OR 5.43 (CI not reported)

Menkes 1986 *(Continued)*

	Batieha 1993 *Reference category:* highest tertile *Results:* Cervical cancer • Lowest tertile: OR 1.12 (95% CI 0.50 to 2.53) Helzlsour 1989 *Reference category:* highest tertile *Results:* Bladder cancer • Both genders: lowest tertile: OR 2.06 (95% CI 0.67 to 6.35) Burney 1989 *Reference category:* highest tertile *Results:* Pancreatic cancer • Both genders: lowest tertile: OR 4.5 (CI not reported) (unmatched analysis) • Both genders: lowest tertile vs higher 2 tertiles: OR 3.90 (95% CI 1.13 to 13.2) (matched analysis) • Male: 12.5 (95% CI 1.8 to 84.0) (unmatched analysis) • Female: 1.2 (95% CI 0.6 to 2.5) (unmatched analysis) Ko 1994 *Reference category:* highest quartile *Results:* Colon cancer • Both genders: lowest quartile: OR 0.82 (95% CI 0.35 to 1.92)
Selenium levels in exposure categories	Menkes 1986b • Quintiles: n.r. Helzlsouer 1986 *Women* • Lowest tertile: ≤ 105.0 µg/L • Highest tertile: ≥ 116.1 µg/L Breslow 1995 • Tertiles: n.r. Zheng 1993 • Tertiles: n.r. Batieha 1993 *Women* • Lowest tertile: ≤ 0.109 ppm • Highest tertile: ≥ 0.124 ppm Helzlsour 1989 *Both genders* • Lowest tertile: ≤ 109.0 µg/L • Highest tertile: ≥ 119.1 µg/L Burney 1989 • Lowest: 0.99 to 1.26 µmol/L; highest: 1.44 to 1.81 µmol/L Ko 1994 • Lowest quartile: ≤ 99.0 µg/L • Highest quartile: ≥ 118.1 µg/L
Notes	*Primary publication:* Menkes 1986b

Menkes 1986 *(Continued)*

	Other publications: Helzlsour 1996, Breslow 1995, Zheng 1993, Batieha 1993, Helzlsour 1989, Burney 1989, Ko 1994, Schober 1987 (cases included in Ko 1994), Menkes 1986a (case included in Menkes 1986b)

Michaud 2002

Methods	Matched, nested case-control study *Country:* Finland
Participants	*Participants:* 29,133 men *Inclusion criteria:* 50 to 69 years of age; smokers; no history of cancer (other than non-melanoma skin cancer) at baseline; no severe physical or psychiatric illness; intake of vitamin E/A/beta-carotene supplements in excess of defined amounts *Name of parent cohort:* Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study *Recruitment*: 1985 to 1988 *Outcome assessment*: 30 April 1993 *Number of cases:* • Bladder cancer: 133 (male/female: 133/0) *Case definition:* incidence *Years of follow-up:* 5 to 8 *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* smoking dose and duration *Variables controlled by matching:* age, year/month of sample collection, intervention group status in RCT (only male smokers included in cohort)
Risk estimates [95% CI]	*Reference category:* lowest tertile/quartile *Results:* Bladder cancer • Male: highest tertile: OR 0.90 (95% CI 0.45 to 1.78) • Male: highest quartile: OR 0.87 (95% CI 0.30 to 2.52)
Selenium levels in exposure categories	n.r.
Notes	

Michaud 2005

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 101,950 (male/female: 33,737/68,213) *Inclusion criteria:* cohort of HPFS (men) and NHS (women); no history of cancer at baseline *Name of parent cohort:* Health Professional Follow-Up Study (HPFS) and Nurses' Health Study (NHS)

Michaud 2005 *(Continued)*

	Recruitment: 1987 (HPFS), 1983 (NHS) *Outcome assessment*: 2000 *Number of cases:* • Bladder cancer: 337 (male/female: 221/116) *Case definition:* incidence *Years of follow-up:* 13 to 17 *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* pack-years of smoking, heavy smoking at baseline *Variables controlled by matching:* age, gender, smoking status, month of sample collection
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Bladder cancer • Male: highest quartile: OR 1.17 (95% CI 0.66 to 2.07) • Female: highest quartile: OR 0.36 (95% CI 0.14 to 0.91)
Selenium levels in exposure categories	Men • Lowest quartile: ≤ 0.722 µg/g • Highest quartile: ≥ 0.912 µg/g Women • Lowest quartile: ≤ 0.686 µg/g • Highest quartile: ≥ 0.840 µg/g
Notes	

Muka 2017

Methods	Cohort study *Country:* the Netherlands
Participants	*Name of parent cohort:* The Rotterdam Study *Participants:* 5435 (male/female: n.r.) *Inclusion criteria:* aged ≥ 55 and living in the Ommoord district *Recruitment:* 1989 to 1993 *Outcome assessment:* December 2011 *Number of cases:* 211 (male/female: 128/83) *Case definition:* incidence *Years of follow-up:* mean: 15.2 *Type of selenium marker:* intake
Interventions	d.n.a.

Muka 2017 *(Continued)*

Outcomes	*Analysed cases:* 211 (male/female: 128/83) *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, sex, alcohol intake, body mass index, smoking status, physical activity, Dutch healthy diet index, dietary processed meat intake, dietary unprocessed red meat intake, total energy intake, hormone replacement therapy, diabetes mellitus, education status, income status, total energy, adjusted sum of other minerals (excluding selenium), and family history of cancer
Risk estimates [95% CI]	*Reference category:* lowest tertile *Results:* Lung cancer • Highest tertile: HR 1.39 (95% CI 0.97 to 1.99)
Selenium levels in exposure categories	n.r.
Notes	Lung cancer: highest tertile: HR 1.44 (95% CI 0.98 to 2.11) after exclusion of lung cancer within the first 2 years of follow-up

Nomura 1987

Methods	Unmatched, nested case-control study *Country:* United States
Participants	*Participants:* 6860 men *Inclusion criteria:* born 1900 to 1919; Japanese ancestry; inhabitants of Oahu/Hawaii; participants in the Honolulu Heart Program (1965 to 1968) *Name of parent cohort:* Honolulu Heart Program *Recruitment*: 1971 to 1975 *Outcome assessment*: n.r. *Number of cases:* • Any cancer: 280 (male/female: 280/0) • Stomach cancer: 66 (male/female: 66/0) • Rectal cancer: 32 (male/female: 32/0) • Lung cancer: 71 (male/female: 71/0) • Colon cancer: 82 (male/female: 82/0) • Bladder cancer: 29 (male/female: 29/0) *Case definition:* incidence *Years of follow-up:* 11 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* proportional hazard regression/Cox regression *Variables controlled in analysis:* • Age at examination, cigarettes/d (any cancer, lung cancer, bladder cancer) • Age at examination (stomach, rectum, colon)
Risk estimates [95% CI]	*Reference category*: highest quintile

Nomura 1987 *(Continued)*

	Results: Stomach cancer • Male: lowest quintile: OR 0.9 (CI not reported) Rectal cancer • Male: lowest quintile: OR 1.6 (CI not reported) Lung cancer • Male: lowest quintile: OR 1.1 (CI not reported) Colon cancer • Male: lowest quintile: OR 1.8 (CI not reported) Bladder cancer • Male: lowest quintile: OR 3.1 (CI not reported) All five types of cancer • Male: lowest quintile: OR 1.3 (CI not reported)
Selenium levels in exposure categories	Lowest quintile: ≤ 103.0 µg/L Highest quintile: ≥ 133.1 µg/L
Notes	N.B.: "Any cancer" in this study comprises all cancer cases for stomach, rectal, lung, colon, and bladder cancer.

Nomura 2000

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 9345 men *Inclusion criteria:* no cancer diagnosis at baseline, blood sample available for analysis, men from 2 cohorts: subcohort 1: participants of Nomura 1987; subcohort 2: brothers of participants in Nomura 1987 *Recruitment*: 1971 to 1977 *Outcome assessment*: 1995 *Number of cases:* • Prostate cancer: 249 (male/female: 249/0) *Case definition:* incidence *Years of follow-up:* 19 to 25 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* random sample of 249 (out of 360) because of limited resources *Statistical methods:* generalised linear model *Variables controlled in analysis:* cigarette smoking history, age *Variables controlled by matching:* age, year/month of sample collection, recruitment in subcohort 1 or 2
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Prostate cancer • Highest quartile: OR 0.5 (95% CI 0.3 to 0.9)
Selenium levels in exposure categories	Lowest quartile: ≤ 119.29 µg/L Highest quartile: ≥ 147.20 µg/L

Nomura 2000 *(Continued)*

Notes	

NPCT 2002

Methods	Randomised controlled trial Nutritional Prevention of Cancer Trial (NPCT) *Allocation:* random, block/stratified by clinic *Sequence generation:* computer-generated random numbers *Concealment:* central assignment (sealed pill bottles) *Blinding:* participant blinded, doctor blinded, outcome assessor/pathologist unclear, review/coding of medical records blinded *Dropouts/withdrawals:* "9 patients (5 in the selenium group and 4 in the placebo group) declined to provide additional illness information" (Clark 1996, p. 1959) - 0 participants lost to vital follow-up *Intention-to-treat-analysis:* yes *Recruitment period:* 1983 to 1991 *End of predefined study period:* 31 December 1993 *Blinded intervention continued until end of blinded period:* 31 January 1996 *Intervention duration:* • 31 December 1993 (end of study period): mean = 4.5 years • 31 January 1996 (end of blinded period): mean = 7.9 years *Observation period/dermatological follow-up:* • 31 December 1993 (end of study period): mean = 6.4 years • 31 January 1996 (end of blinded period): mean = 7.4 years *Detection of cases:* dermatological examination and interview every 6 months during follow-up; incident BCC and SCC diagnosed by biopsy and confirmed by another dermatopathologist *Informed consent:* written informed consent forms, approval by institutional review board of participating institutions
Participants	*Country:* United States *Participants:* 1312 (randomised to selenium group: 653; to placebo group: 659) *Condition:* male and female participants with history of 2 or more squamous cell or basal cell skin cancers *Demographics:* mean age 63.4 years (selenium)/63.0 years (placebo); 73.8% men (selenium), 75.6% men (placebo) *Recruitment and setting:* 7 dermatological clinics (3 academic units, 4 private practices) in the United States
Interventions	*Intervention:* 200 µg selenium supplied as 500 mg selenium yeast tablets p.o. daily *Control:* placebo

NPCT 2002 *(Continued)*

Outcomes	*Primary outcome measure:* incidence of basal and squamous cell carcinoma of the skin: • All analyses were based on 1250 participants with initial blood collection within 4 days after randomisation (621 in the selenium group and 629 in the placebo group) *Other reported outcomes and secondary outcome measures:* • Reported in Clark 1996: incidence of lung cancer, prostate cancer, colorectal cancer, any cancer, head and neck cancer, bladder cancer, oesophageal cancer, breast cancer, melanoma, haematological cancer • Reported in Duffield-Lillico 2002: overall cancer mortality
Risk estimates [95% CI]	*Primary outcomes:* At end of study period (31 December 1993) (Clark 1996) • BCC: RR 1.10 (95% CI 0.95 to 1.28); cases: selenium group: 377, placebo group: 350; incidence per person-year under follow-up: selenium group 0.16, placebo group 0.15 • SCC: RR 1.14 (95% CI 0.93 to 1.39); cases: selenium group 218, placebo group: 190; incidence per person-year under follow-up: selenium group 0.07, placebo group 0.06 At end of blinded period (31 January 1996) (Duffield-Lillico 2003) • BCC: RR 1.17 (95% CI 1.02 to 1.35), HR 1.09 (95% CI 0.94 to 1.26); number of cases not reported; incidence per person-year under follow-up: selenium group: 0.16, placebo group 0.13 • SCC: RR 1.32 (95% CI 1.09 to 1.60), HR 1.25 (95% CI 1.03 to 1.51); number of cases not reported; incidence per person-year under follow-up: selenium group: 0.05, placebo group 0.07 • NMSC: RR 1.27 (95% CI 1.11 to 1.45), HR 1.17 (95% CI 1.02 to 1.34); number of cases not reported; incidence per person-year under follow-up: selenium group: 0.20, placebo group 0.16 *Other reported outcomes and secondary outcomes:* At end of study period (31 December 1993) (Clark 1996) • Lung cancer: RR 0.54 (95% CI 0.30 to 0.98), adjusted HR 0.56 (95% CI 0.31 to 1.01) cases selenium: 17, placebo: 31 • Prostate cancer: RR 0.37 (95% CI 0.18 to 0.71), adjusted HR 0.35 (95% CI 0.18 to 0.65) cases selenium: 13, placebo: 35 • Colorectal cancer: RR 0.42 (95% CI 0.18 to 0.95), adjusted HR 0.39 (95% CI 0.17 to 0.90) cases selenium: 8, placebo: 19 • Any cancer: RR 0.63 (95% CI 0.47 to 0.85), adjusted HR 0.61 (95% CI 0.46 to 0.82) cases selenium: 77, placebo: 119 • Head and neck cancer: RR 0.74 (95% CI 0.21 to 2.43), adjusted HR 0.77 (95% CI 0.27 to 2.24) cases selenium: 6, placebo: 8 • Bladder cancer: RR 1.32 (95% CI 0.40 to 4.61), adjusted HR 1.27 (95% CI 0.44 to 3.67) cases selenium: 8, placebo: 6 • Oesophageal cancer: RR 0.33 (95% CI 0.03 to 1.84), adjusted HR 0.30 (95% CI 0.06 to 1.49) cases selenium: 2, placebo: 6 • Breast cancer: RR 2.88 (95% CI 0.72 to 16.5), adjusted HR 2.95 (95% CI 0.80 to 10.9) cases selenium: 9, placebo:3 • Melanoma: RR 0.97 (95% CI 0.32 to 2.96), adjusted HR 0.92 (95% CI 0.34 to 2.45) cases selenium: 8, placebo: 8

NPCT 2002 *(Continued)*

	• Haematological cancer: RR 1.58 (95% CI 0.46 to 6.14), adjusted HR 1.50 (95% CI 0.49 to 4.60) cases selenium: 8, placebo: 5 • Other specific carcinomas: RR 0.55 (95% CI 0.14 to 1.82), adjusted HR 0.54 (95% CI 0.18 to 1.62), cases selenium: 5, placebo: 9 • Total carcinoma: RR 0.55 (95% CI 0.40 to 0.77), adjusted HR 0.54 (95% CI 0.39 to 0.75), cases selenium: 59; placebo: 104 • Leukaemia/lymphoma: RR 1.58 (95% CI 0.46 to 6.14), adjusted HR 1.50 (95% CI 0.49 to 4.60), cases selenium: 8, placebo 5 • Other specific non-carcinomas: RR 0.99 (95% CI 0.13 to 7.37), HR 0.99 (95% CI 0.20 to 4.94), cases selenium: 3, placebo: 3 • Total non-carcinomas: RR 1.17 (95% CI 0.57 to 2.44), adjusted HR 1.16 (95% CI 0.60 to 2.27), cases selenium: 19; placebo: 16 At end of blinded period (31 January 1996) (Duffield-Lillico 2002) • Lung cancer: RR 0.70 (95% CI 0.40 to 1.21), adjusted HR 0.74 (95% CI 0.44 to 1.24), cases selenium: 25, placebo: 35 • Prostate cancer: RR 0.51 (95% CI 0.29 to 0.87), adjusted HR 0.48 (95% CI 0.28 to 0.80), cases selenium: 22, placebo: 42 • Colorectal cancer: RR 0.46 (95% CI 0.19 to 1.08), adjusted HR 0.46 (95% CI 0.21 to 1.02), cases selenium: 9, placebo: 19 • Any cancer: RR 0.75 (95% CI 0.58 to 0.98), adjusted HR 0.75 (95% CI 0.58 to 0.97), cases selenium: 105, placebo: 137 • Head and neck cancer: RR 1.27 (95% CI 0.42 to 4.01), adjusted HR 1.27 (95% CI 0.47 to 3.42), cases selenium: 9, placebo: 7 • Bladder cancer: RR 1.24 (95% CI 0.44 to 3.61), adjusted HR 1.28 (95% CI 0.50 to 3.25), cases selenium: 10, placebo: 8 • Oesophageal cancer: RR 0.39 (95% CI 0.04 to 2.41), adjusted HR 0.40 (95% CI 0.08 to 2.07), cases selenium: 2, placebo: 5 • Breast cancer: RR 1.82 (95% CI 0.62 to 6.01), adjusted HR 1.89 (95% CI 0.69 to 5.14), cases selenium: 11, placebo: 6 • Melanoma: RR 1.21 (95% CI 0.46 to 3.30), adjusted HR 1.18 (95% CI 0.49 to 2.85), cases selenium: 11, placebo: 9 • Haematological cancer (lymphoma and leukaemia): RR 1.32 (95% CI 0.40 to 4.61), adjusted HR 1.25 (95% CI 0.43 to 3.61), cases selenium: 8, placebo: 6 • Cancer mortality, all sites: RR 0.59 (95% CI 0.39 to 0.89), adjusted HR 0.59 (95% CI 0.39 to 0.87), cases selenium: 40, placebo: 66 • Other carcinomas: RR 0.66 (95% CI 0.19 to 2.07), adjusted HR 0.67 (95% CI 0.24 to 1.88), cases selenium: 6, placebo:9 • Other non-carcinomas: RR 0.59 (95% CI 0.09 to 3.04), adjusted HR 0.59 (95% CI 0.14 to 2.47), cases selenium: 3, placebo: 5
Selenium levels in exposure categories	d.n.a.
Notes	*Adverse effects:* Clark 1996: 35 participants (21 in selenium and 14 in control group) complained of adverse effects, mostly involving gastrointestinal upset, and withdrew treatment.

NPCT 2002 *(Continued)*

	Post hoc introduced secondary outcomes: all-cause mortality, total cancer mortality, total cancer incidence, and incidence of lung/prostate/colorectal cancers *HR:* adjusted for sex, age, smoking status, clinic site, plasma selenium concentration, clinical sun damage, sunscreen use at baseline, and number of BCCs/SCCs/NMSCs in the 12 months before randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random, block/stratified by clinic, computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central assignment (sealed pill bottles)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Occurrence of a detection bias, namely, a considerably higher rate of prostate biopsy in the placebo group
Selective reporting (reporting bias)	Low risk	No problems found

O'Grady 2014

Methods	Cohort study *Country:* United States
Participants	*Name of parent cohort:* National Institute of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study *Participants:* 482,807 (male/female: 287,944/194,863) *Inclusion criteria:* 50 to 71 years of age, AARP members, no previous diagnosis of cancer other than NMSC *Recruitment:* 1995 to 1996 *Outcome assessment:* December 2006 *Number of cases:* 592 (male/female: 257/335) *Case definition:* incidence *Years of follow-up:* mean: 9.1 *Type of selenium marker:* intake
Interventions	d.n.a.
Outcomes	*Analysed cases:* • Total thyroid cancer: 592 (male/female: 257/335) • Papillary thyroid cancer subtype: 406 (male/female: 164/242) • Follicular thyroid cancer subtype: 113 (male/female: 57/56) *Statistical methods:* Cox proportional hazard model

O'Grady 2014 *(Continued)*

	Variables controlled in analysis: entry age, sex, calories, smoking status, race, education, BMI, physical activity, vitamin C, vitamin E, beta-carotene, and folate
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Total thyroid cancer • Both genders: highest quintile: HR 1.35 (95% CI 0.99 to 1.84) • Male: highest quintile: HR 1.23 (95% CI 0.71 to 2.12) • Female: highest quintile: HR 1.14 (95% CI 0.65 to 2.02) Papillar subtype • Both genders: highest quintile: HR 1.35 (95% CI 0.92 to 1.98) • Male: highest quintile: HR 1.32 (95% CI 0.65 to 2.69) • Female: highest quintile: HR 1.29 (95% CI 0.68 to 2.46) Follicular subtype • Both genders: highest quintile: HR 1.41 (95% CI 0.71 to 2.79) • Male: highest quintile: HR 1.32 (95% CI 0.43 to 4.03) • Female: highest quintile: HR 0.88 (95% CI 0.20 to 3.87)
Selenium levels in exposure categories	Lowest quintile: median 47 µg/d Highest quintile: median 150.1 µg/d
Notes	

Outzen 2016

Methods	Matched, nested case-control study *Country:* Denmark
Participants	*Name of parent cohort:* Danish Prospective Diet, Cancer and Health Study *Participants:* 27,179 men *Inclusion criteria:* aged 50 to 64, born in Denmark, residents in the Copenhagen and Aarhus areas, no previous history of cancer *Recruitment:* December 1993 to May 1997 *Outcome assessment:* 31 December 2007 *Number of cases:* 911 (male/female: 911/0) *Case definition:* incidence *Years of follow-up:* 8 *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Analysed cases:* Prostate cancer • 784 (male/female: 784/0) *Statistical methods:* conditional logistical regression

Outzen 2016 *(Continued)*

	Variables controlled in analysis: body mass index, education, smoking status, duration and frequency, and participation in sport *Variables controlled by matching:* age at blood collection, time of day of blood collection, and fasting status
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Prostate cancer • Highest quartile: OR 0.95 (95% CI 0.70 to 1.29)
Selenium levels in exposure categories	Lowest quartile: ≤ 71.4 µg/d Highest quartile: > 88.9 µg/d
Notes	

Overvad 1991

Methods	Cohort/subcohort controlled cohort study *Country:* Channel Islands (UK)
Participants	*Participants:* 5162 women *Inclusion criteria:* ≥ 35 years of age; ostensibly healthy inhabitants of Guernsey *Name of parent cohort:* Channel Island Cohort *Recruitment*: 1967 to 1976 *Outcome assessment*: end of 1985 *Number of cases:* • Breast cancer: 46 (male/female: 0/46) *Case definition:* incidence *Years of follow-up:* mean: 11 years for cases *Type of selenium marker:* plasma
Interventions	d.n.a.
Outcomes	*Analysed cases:* 46 of 88 (reason for non-inclusion: no plasma available) *Statistical methods:* logistical regression *Variables controlled in analysis:* age, age at menarche, age at first baby, parity, BMI
Risk estimates [95% CI]	*Reference category:* highest quartile *Results:* Breast cancer • Lowest quartile: RR 0.80 (95% CI 0.29 to 2.19)
Selenium levels in exposure categories	Lowest quartile: ≤ 84.90 µg/L Highest quartile: ≥ 116.00 µg/L
Notes	

Pantavos 2015

Methods	Cohort study *Country:* the Netherlands
Participants	*Name of parent cohort:* The Rotterdam Study *Participants:* 4877 women *Inclusion criteria:* aged ≥ 55 and living in the Ommoord district. no history of previous breast cancer *Recruitment:* July 1989 to September 1993 *Outcome assessment:* December 2010 *Number of cases:* 199 (male/female: 0/199) *Case definition:* incidence *Years of follow-up:* median: 17 years *Type of selenium marker:* intake
Interventions	d.n.a.
Outcomes	*Analysed cases:* 199 (male/female: 0/199) *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, body mass index, education level, family history of breast cancer, smoking status, alcohol consumption, use of multi-vitamin supplement
Risk estimates [95% CI]	*Reference category:* lowest tertile *Results:* Breast cancer • Highest tertile: HR 1.34 (95% CI 0.94 to 1.91)
Selenium levels in exposure categories	Lowest tertile: median 23.58 µg/d Highest tertile: median 37.46 µg/d
Notes	

Park 2015

Methods	Cohort study *Country:* United States (Hawaii and California)
Participants	*Name of parent cohort:* The Multiethnic Cohort *Participants:* 75,216 men *Inclusion criteria:* aged 45 to 75, African Americans, Native Hawaiians, Japanese American, Latinos, and white men, without a previous diagnosis of prostate cancer *Recruitment:* 1993 to 1996 *Outcome assessment:* 31 December 2010

Park 2015 *(Continued)*

	Number of cases: • Prostate cancer: 7115 *Case definition:* incidence *Years of follow-up:* mean: 13.9 *Type of selenium marker:* intake
Interventions	d.n.a.
Outcomes	*Analysed cases:* • Prostate cancer: 7115 *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age at entry, race/ethnicity, family history of prostate cancer, body mass index, height, smoking status, education level, history of diabetes, physical activity, daily intakes of alcohol, calcium, legume, and lycopene
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Prostate cancer • Highest quintile: RR 1.01 (95% CI 0.84 to 1.20)
Selenium levels in exposure categories	Lowest quintile: < 44.0 µg/1000 kcal/d Highest quintile ≥ 60.1 µg/1000 kcal/d
Notes	

Peleg 1985

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 2530 men and women *Inclusion criteria:* 15 years of age and older; residents of Evans County; cases within first 2 years of follow-up excluded *Name of parent cohort:* Evans County Study *Recruitment*: 1967 to 1969 *Outcome assessment*: January 1981 *Number of cases:* • Any cancer: 130 (male/female: 78/52) *Case definition:* incidence *Years of follow-up:* 11 to 14 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* n.r.

Peleg 1985 *(Continued)*

	Variables controlled by matching: age, gender, race/ethnicity, year/month of sample collection
Risk estimates [95% CI]	*Reference category:* highest quartile *Results:* Any cancer • Both genders: lowest quartile: OR 1.0 (CI not reported)
Selenium levels in exposure categories	Lowest quartile: ≤ 103 µg/L Highest quartile: ≥ 127 µg/L
Notes	

Peters 2007

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 26,975 white non-Hispanic men *Inclusion criteria:* 55 to 74 years of age; excluded: no baseline questionnaire/informed consent/blood sample, no further contact after screening *Name of parent cohort:* Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial *Recruitment*: September 1993 to June 2001 *Outcome assessment*: 1 October 2001 *Number of cases:* • Prostate cancer: 724 (male/female: 724/0) *Case definition:* incidence *Years of follow-up:* 0.3 to 8.0 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 724 of 803 (reason for non-inclusion: no selenium measurement available) *Statistical methods:* n.r. *Variables controlled in analysis:* age, time since initial screening, year of blood collection, study centre *Variables controlled by matching:* age, month of sample collection, time since initial screening
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Prostate cancer • Highest quartile: OR 0.84 (95% CI 0.62 to 1.14)
Selenium levels in exposure categories	Lowest quartile: 50.5 to 126.7 µg/L Highest quartile: 158.0 to 253.0 µg/L
Notes	

Peters 2008

Methods	Cohort study *Country:* United States
Participants	*Inclusion criteria:* aged 50 to 76 years, participants recruited from subscribers to commercial mailing list, residents of western Washington state, non-whites excluded, no malignant disease at baseline *Name of parent cohort:* Vitamins and Lifestyle (VITAL) study *Recruitment:* 1 October 2000 to 31 December 2002 *Type of selenium marker:* supplemental intake (questionnaire: use of supplements over past 10 years, mean supplemental intake/day calculated) *Case definition:* incidence Peters 2008 *Participants:* 35,242 men *Outcome assessment*: 31 December 2004 *Number of cases:* • Prostate cancer: 818 (male/female: 818/0) *Years of follow-up:* 2 to 4 Asgari 2009 *Participants:* 69,671 men and women *Outcome assessment:* 31 December 2006 *Number of cases:* • Melanoma: 461 (male/female: n.r.) *Years of follow-up:* 4 to 5 years
Interventions	d.n.a.
Outcomes	Peters 2008 *Analysed cases:* 818 of 830 (reason for non-inclusion: not reported) *Statistical methods:* Cox proportional hazard regression analysis *Variables controlled in analysis:* age, family history of prostate cancer, BPH, income, multi-vitamin use Asgari 2009 *Analysed cases:* 1 case not analysed (reason for non-inclusion: not reported) *Statistical methods:* Cox proportional hazard regression *Variables controlled in analysis:* age, sex, education, family history of melanoma, personal history of non-melanoma skin cancer, mole removal, freckles, sunburns, hair colour, reaction to sunlight exposure
Risk estimates [95% CI]	*Reference category:* no supplemental selenium intake (lowest exposure category) Peters 2008 *Results:* Prostate cancer • Highest exposure category: RR 0.90 (95% CI 0.62 to 1.30)

Peters 2008 *(Continued)*

	Asgari 2009 *Results:* Melanoma • Highest exposure category HR 0.98 (95% CI 0.69 to 1.41)
Selenium levels in exposure categories	Stratification according to supplemental selenium intake Peters 2008 • Lowest category: no supplemental intake • Highest category ≥ 51 µg/d Asgari 2009 • Lowest exposure category: no supplemental intake • Highest exposure category ≥ 50 µg/d
Notes	

Ratnasinghe 2000

Methods	Matched, nested case-control study *Country:* China
Participants	*Participants:* 9143 men *Inclusion criteria:* 35 years or older; tin miners employed by the Yunnan Tin Corporation; 10 or more years of underground mining/smelting; no history of cancer at baseline *Recruitment:* 1992 to 1997 *Outcome assessment:* 1997 *Number of cases:* • Lung cancer: 108 (male/female: 108/0) *Case definition:* incidence *Years of follow-up:* ≈ 3 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* plasma available for 108 of a total of 339 identified cases *Statistical methods:* logistical regression, conditional logistical regression, Wilcoxon rank sum test *Variables controlled in analysis:* radon exposure, smoking *Variables controlled by matching:* age, year and month of sample collection
Risk estimates [95% CI]	*Reference category:* lowest tertile *Results:* Lung cancer • Highest tertile: OR 1.2 (95% CI 0.6 to 2.4)
Selenium levels in exposure categories	Lowest tertile: 20 to 39 µg/L Highest tertile: 55 to 121 µg/L
Notes	

Reid 2008

Methods	Randomised controlled trial Substudy of the Nutritional Prevention of Cancer Trial (NPCT 2002) *Allocation:* random *Sequence generation:* computer-generated random numbers *Concealment:* central assignment (sealed pill bottles) *Blinding:* participant blinded, doctor blinded, outcome assessor/pathologist unclear, review/coding of medical records blinded *Dropouts/withdrawals:* 2 participants declined to provide additional illness information, no participant lost to vital follow -up *Intention-to-treat-analysis:* yes *Recruitment period:* 1989-1992 *Treatment duration:* • Blinded intervention continued until the end of the blinded period; 1 February 1996. *Observation period/dermatological follow-up:* 1 February 1996 *Detection of cases:* dermatological examination and interview every 6 months during follow-up; incident BCC and SCC diagnosed by biopsy and confirmed by another dermatopathologist *Informed consent:* written informed consent forms, approval by institutional review boards of participating institutions
Participants	423 male and female participants with prior non-melanoma skin cancer *Country:* United States *Participants:* 423 (randomised to selenium group: 210, to placebo group: 213) *Condition:* male and female with history of 2 or more squamous cell or basal cell skin cancers *Demographics:* mean age 63.8 years (selenium)/63.8 years (placebo); 66.2% men (selenium). 68.2% men (placebo) *Recruitment and setting:* dermatological clinic in Macon, Georgia
Interventions	*Intervention:* • 400 µg selenium supplied as selenium yeast tablets p.o. daily *Control:* • Placebo • 400 µg/d of selenium yeast or identical-appearing low selenium yeast placebo *Recruitment:* 12 September 1989 to 3 April 1992 *End of blinded treatment period:* 2 February 1996
Outcomes	*Primary outcome measure:* incidence of basal and squamous cell carcinoma of the skin

Reid 2008 *(Continued)*

	• All analyses were based on n = 423 participants with initial blood collection within 4 days after randomisation *Other reported outcomes:* • Total internal cancer incidence
Risk estimates [95% CI]	*Primary outcomes:* • BCC: RR 0.90 (95% CI 0.65 to 1.24); cases: selenium group: 76, placebo group: 83; adjusted HR: 0.95 (95% CI 0.69 to 1.29) • SCC: RR 1.05 (95% CI 0.71 to 1.56); cases: selenium group: 56, placebo group: 53; adjusted HR: 1.05 (95% CI 0.72 to 1.53) • NMSC: RR 0.88 (95% CI 0.66 to 1.16); cases: selenium group: 98, placebo group: 108; adjusted HR: 0.91 (95% CI 0.69 to 1.20) • NMSC in women: RR 0.40 (95% CI 0.20 to 0.80) *Other reported outcomes:* • Total internal cancer incidence: RR 1.10 (95% CI 0.57 to 2.17); cases: selenium group: 21, placebo group: 19
Selenium levels in exposure categories	d.n.a.
Notes	Information on study design, which was not reported in Reid 2008, was taken from information available on the Nutritional Prevention of Cancer Trial. *Adverse effects:* not reported *HR:* adjusted for: age (continuous), smoking status (never, former, current), gender

Ringstad 1988

Methods	Matched, nested case-control study *Country:* Norway
Participants	*Participants:* 9364 men and women *Inclusion criteria:* 20 to 54 years of age (men), 20 to 49 years of age (women); inhabitants of Tromso; blood sample provided in 1979; no history of cancer at baseline *Name of parent cohort:* Tromso Heart Study II *Recruitment*: 1979 to 1980 *Outcome assessment*: 1985 *Number of cases:* • Any cancer: 60 (male/female: 26/34) *Case definition:* incidence *Years of follow-up:* 5 to 7 *Type of selenium marker:* serum
Interventions	d.n.a.

Ringstad 1988 *(Continued)*

Outcomes	*Analysed cases:* 60 of 72 (reason for non-inclusion: no sample available) *Statistical methods:* n.r. *Variables controlled by matching:* age, gender, smoking status, month of sample collection, place of residence (district of Tromso)
Risk estimates [95% CI]	*Reference category:* highest 3 quartiles *Results:* Any cancer • Both genders: lowest quartile: OR 1.4 (95% CI 0.6 to 3.5)
Selenium levels in exposure categories	Lowest quartile: ≤ 114.49 µg/L Highest 3 quartiles: 114.50 to 114.51 µg/L
Notes	

Sakoda 2005

Methods	Matched, nested case-control study *Country:* China
Participants	*Participants:* 41,563 men and women *Inclusion criteria:* inhabitants of Haiman city of Chinese origin; written consent; toenail clipping available *Recruitment:* January 1993 to December 1993 *Outcome assessment:* 30 September 2000 *Number of cases:* • Primary liver cancer: 166 (male/female: 154/12) *Case definition:* mortality *Years of follow-up:* 6.8 to 7.8 *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Analysed cases:* 166 of 455 observed cases (only cases with questionnaire, blood sample, and toenail specimen analysed after 2000 owing to different methods of selenium analysis) *Statistical methods:* not specified *Variables controlled in analysis:* • Both genders: age, gender, HBsAg status, alcohol intake, history of acute hepatitis, occupation • Men: age, HBs-Ag status, alcohol intake, history of acute hepatitis, family history of HCC, occupation • Women: HBs-Ag status, age, history of acute hepatitis *Variables controlled by matching:* age, gender, township of residence
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Primary liver cancer • Both genders: highest quartile: OR 0.50 (95% CI 0.28 to 0.90) • Male: highest quartile: OR 0.57 (95% CI 0.31 to 1.05) • Female: highest 3 quartiles: OR 0.18 (95% CI 0.03 to 1.13)

Sakoda 2005 *(Continued)*

Selenium levels in exposure categories	Both genders and men • Lowest quartile: 0 to 1.70 ppm • Highest quartile: ≥ 4.43 ppm Women • Lowest quartile: 0.00 to 1.70 ppm • Highest 3 quartiles: ≥ 1.71 ppm
Notes	

Salonen 1984

Methods	Matched, nested case-control study *Country:* Finland
Participants	*Participants:* 8113 men and women *Inclusion criteria:* 31 to 59 years of age; random sample of inhabitants of 2 Finnish provinces; initially free of cancer *Name of parent cohort:* North Karelia Project *Recruitment*: February to April 1972 *Outcome assessment*: 31 December 1978 *Number of cases:* • Any cancer: 128 (male/female: n.r.) *Case definition:* incidence *Years of follow-up:* 8.5 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* logistical regression/paired-sample OR *Variables controlled in analysis:* tobacco consumption, serum cholesterol, beer consumption, dietary saturated fats, years of education, study area *Variables controlled by matching:* age, gender, smoking (tobacco use/d), total serum cholesterol
Risk estimates [95% CI]	*Reference category:* above 30th percentile *Results:* Any cancer • Both genders: ≤ 30th percentile: OR 3.1 (95% CI 1.5 to 7.7) • Both genders: ≤ 0 percentile: OR 3.0 (95% CI 1.2 to 21.9)
Selenium levels in exposure categories	1st to 10th percentile ≤ 34.00 µg/L Above 30th percentile ≥ 45.00 µg/L
Notes	

Salonen 1985

Methods	Matched, nested case-control study

Salonen 1985 *(Continued)*

	Country: Finland
Participants	*Participants:* 12,155 men and women *Inclusion criteria:* 30 to 64 years of age; random sample of residents of 2 Finnish provinces; initially free of cancer *Name of parent cohort:* North Karelia Project *Recruitment*: January to March 1977 *Outcome assessment:* 31 December 1980 *Number of cases:* • Any cancer: 51 (male/female: 30/21) *Case definition:* mortality *Years of follow-up:* 3.7 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Analysed cases:* 51 out of 56 (reason for non-inclusion: no serum sample available) *Statistical methods:* logistical regression *Variables controlled by matching:* age, gender, smoking (tobacco use/d)
Risk estimates [95% CI]	*Reference category:* highest 2 tertiles *Results:* Any cancer • Both genders: lowest tertile: OR 5.8 (95% CI 1.2 to 29.0)
Selenium levels in exposure categories	Lowest tertile: ≤ 47.00 µg/L Highest 2 tertiles ≥ 47.10 µg/L
Notes	

SELECT 2009

Methods	Randomised controlled trial SELECT (Selenium and Vitamin E Cancer Prevention Trial) *Allocation:* random, block/stratified by clinic *Sequence generation:* computer-generated random numbers *Concealment:* central assignment (pill bottles) *Blinding:* participant blinded, doctor blinded, outcome assessor/pathologist blinded, review/coding of medical records blinded *Dropouts/withdrawals:* of 35,533 randomised participants, 645 were excluded from analysis because they had prior prostate cancer, did not give informed consent, or participated at 2 study sites that were excluded owing to management and regulatory issues *Intention-to-treat-analysis:* yes *Recruitment period:* 22 August 2001 to 24 June 2004 *End of study period:* 1 August 2009

SELECT 2009 *(Continued)*

	Blinded intervention was discontinued on 23 October 2008 following the recommendation of the Data Safety and Monitoring Committee after the second formal interim analysis in September 2008. *Detection of cases:* Participants had clinic visits once every 6 months and reported prostate cancers to the study staff. Study staff obtained medical records to verify the diagnosis. Tissue and the corresponding pathology report were sent to the central pathology laboratory for confirmation. *Informed consent:* yes
Participants	*Countries:* United States, Canada, Puerto Rico *Number of participants:* 34,888 men, randomised to 4 groups: placebo (8696), vitamin E (8737), selenium (8752), selenium + vitamin E (8703) *Condition:* healthy men, aged 50 years or older (African American) or 55 years or older (all other), no prior diagnosis of prostate cancer, 4 ng/mL or less of PSA in serum, a digital rectal examination not suspicious for cancer, no current use of anticoagulant therapy other than 175 mg/d or less of acetylsalicylic acid, or 81 mg/d or less of acetylsalicylic acid with clopidogrel bisulphate, no history of haemorrhagic stroke, normal blood pressure *Demographics:* median age: 62.3 to 62.6 years in all 4 intervention groups, 79% white in all 4 intervention groups *Recruitment and setting:* 427 participating sites
Interventions	Group 1: placebo + placebo Group 2: 400 IU/d all rac-alpha-tocopheryl acetate + placebo Group 3: 200 µg/d L-selenomethionine + placebo Group 4: 400 IU/d all rac-alpha-tocopheryl acetate + 200 µg/d L-selenomethionine
Outcomes	*Primary outcome:* incidence of prostate cancer as determined by routine clinical management *Secondary outcomes:* incidence of any cancer/lung cancer/colorectal cancer, diabetes mellitus, cardiovascular events, death from any cause
Risk estimates [95% CI]	Results are presented for the comparison of selenium alone (group 3) vs placebo (group 1) *Primary outcome:* • Prostate cancer: HR 1.04 (95% CI 0.90 to 1.18) (99% CI 0.87 to 1.24), cases: selenium 432 (5-year rate: 4.56%), placebo 416 (5-year rate 4.43%) *Secondary outcomes:* • Any cancer: HR 1.01 (95% CI 0.89 to 1.15) • Lung cancer: HR 1.12 (99% CI 0.73 to 1.72) • Colorectal cancer: HR 1.05 (99% CI 0.66 to 1.67) • Other primary cancer (excluding prostate cancer, basal cell and squamous cell skin cancer): HR 0.95 (99% CI 0.77 to 1.17) • Diabetes mellitus: HR 1.07 (99% CI 0.94 to 1.22) • Cardiovascular events: HR 1.02 (99% CI 0.92 to 1.13) • Deaths: HR 0.99 (99% CI 0.82 to 1.19) • Deaths from cancer: HR 1.02 (99% CI 0.74 to 1.41)

SELECT 2009 *(Continued)*

Selenium levels in exposure categories	d.n.a.
Notes	Adverse effects: • Alopecia: RR 1.28 (99% CI 1.01 to 1.62) • Dermatitis grade 1 to 2: RR 1.17 (99% CI 1.00 to 1.35) • Dermatitis grade 3 to 4: RR 1.74 (99% CI 0.56 to 5.44) • Halitosis: RR 1.17 (99% CI 0.99 to 1.38) • Nail changes: RR 1.04 (99% CI 0.94 to 1.16) • Fatigue grade 1 to 2: RR 1.09 (99% CI 0.95 to 1.26) • Fatigue grade 3 to 4: RR 0.87 (99% CI 0.40 to 1.88) • Nausea grade 1 to 2: RR 1.19 (99% CI 0.94 to 1.52) • Nausea grade 3: RR 0.99 (99% CI 0.30 to 3.34)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random, block/stratified by clinic, computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central assignment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, doctors, outcomes
Selective reporting (reporting bias)	Low risk	No problems found

Steevens 2010

Methods	Cohort/subcohort controlled cohort study *Country:* the Netherlands
Participants	*Name of parent cohort:* Netherlands Cohort Study (NLCS) *Recruitment*: 1986 van den Brandt 1993b *Participants:* 120,852 (male/female: 58,279/ 62,573); aged 55 to 69 years; returned baseline questionnaire; no history of cancer at baseline *Outcome assessment*: 31 December 2002 *Number of cases:* • Oesophageal squamous cell carcinoma (ESCC): 64 (male/female: 40/24) • Oesophageal adenocarcinoma (EAC): 112 (male/female: 93/19) • Gastric cardia adenocarcinoma (GCA): 114 (male/female: 97/17)

Steevens 2010 *(Continued)*

	Case definition: incidence *Years of follow-up:* 16.3 *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Analysed cases:* • Oesophageal squamous cell carcinoma (ESCC): 64 of 71 • Oesophageal adenocarcinoma (EAC): 112 of 129 • Gastric cardia adenocarcinoma (GCA): 114 of 127 *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, sex, cigarette smoking (current yes/no, number of cigarettes smoked daily, and number of smoking years), alcohol consumption (g/d), and BMI (kg/m^2)
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Esophageal squamous cell carcinoma (ESCC) • Both genders: highest quartile: RR 0.37 (95% CI 0.16 to 0.86) • Men: highest quartile: RR 0.81 (95% CI 0.64 to 1.4) • Women: highest quartile: RR 0.79 (95% CI 0.63 to 0.99) Oesophageal adenocarcinoma (EAC) • Both genders: highest quartile: RR 0.76 (95% CI 0.41 to 1.40) • Men: highest quartile: RR 1.07 (95% CI 0.99 to 1.15) • Women: highest quartile: RR 0.72 (95% CI 0.61 to 0.84) Gastric cardia adenocarcinoma (GCA) • Both genders: highest quartile: RR 0.52 (95% CI 0.27 to 1.02) • Men: highest quartile: RR 0.94 (95% CI 0.84 to 1.06) • Women: highest quartile: RR 0.73 (95% CI 0.56 to 0.95)
Selenium levels in exposure categories	Lowest quartile: ≤ 0.498 µg/g Highest quartile: ≥ 0.613 µg/g
Notes	

Steinbrecher 2010

Methods	Nested case-control study *Country:* Germany
Participants	*Participants:* 11,928 men (from the total cohort of 25,540 men and women) *Name of parent cohort:* EPIC-Heidelberg cohort *Recruitment*: 1994 to 1998 *Outcome assessment*: 2/2007 *Number of cases:* • Prostate cancer: 248 *Case definition:* incidence *Years of follow-up:* mean: 3

Steinbrecher 2010 *(Continued)*

	Type of selenium marker: serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis: f*amily history of prostate cancer, participation in PSA testing, smoking status, and vigorous physical activity *Variables controlled in matching*: age group and time of recruitment
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Prostate cancer • Highest quartile: OR 1.10 (95% CI 0.58 to 2.09)
Selenium levels in exposure categories	Lowest quartile: ≤ 78.9 µg/L Highest quartile: ≥ 95.0 µg/L
Notes	

Suadicani 2012

Methods	Cohort study *Country:* Denmark
Participants	*Participants:* 3333 males; male participants were derived from 14 workplaces in Copenhagen: the Air Force, Army, Navy, Emergency Management Agency, Postal Service, Customs Service, a railroad company, a national bank, a telephone company, 3 municipal service centres (for electricity and engineering and a fire brigade), a pharmaceutical company, and a building contractor company *Name of parent cohort:* Copenhagen male study *Recruitment*: from 1970 to 1971/1985 to 1986 *Outcome assessment*: 1985 to 1986/2001 *Number of cases:* • Deaths for lung cancer: 167 *Case definition:* death for lung cancer *Years of follow-up:* 16 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox logistical regression *Variables controlled in analysis:* age, pack-years of smoking, spirits intake, and dietary markers
Risk estimates [95% CI]	*Reference category:* lowest exposure category: 0.4 to 1.0 µmol/L *Results:* Deaths from lung cancer • Highest exposure category: HR 1.43 (95% CI 0.96 to 2.14)

Suadicani 2012 *(Continued)*

Selenium levels in exposure categories	Lowest category: 31.58 to 78.96 µg/L Highest category: 120.65 to 236.88 µg/L
Notes	

Sun 2016

Methods	Cohort study *Country:* China
Participants	*Name of parent cohorts:* Shangai Men's Health Study (SMHS) and Shangai Women's Health Study (SWHS) *Participants:* 133,957 (male/female: 61,470/74,941) • SMHS: 61,480 men • SWHS: 74,941 women *Inclusion criteria:* • SMHS: men aged 40 to 74, residents in Shangai with no history of cancer • SWHS: women aged 40 to 70, residents in Shangai with no history of cancer *Recruitment:* • SMHS: April 2002 to June 2006 • SWHS: March 1997 to May 2000 *Outcome assessment:* 31 December 2012 *Number of cases:* 2603 (male/female: 1798/805) *Case definition:* mortality *Years of follow-up:* • SMHS: median: 8.37 • SWHS: median: 13.90 *Type of selenium marker:* intake
Interventions	d.n.a
Outcomes	*Analysed cases:* *Cancer mortality:* 2603 (male/female: 1798/805) *Statistical methods:* Cox proportional hazard model *Variables controlled in analysis:* age, birth cohort, education, income, marital status, occupation, body mass index, physical activity, total energy intake, dietary fat intake, supplement use, smoking status, drinking status, status with regard to history of hypertension, diabetes, coronary hearth disease, or stroke, family history of cancer and menopausal status (women only)
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Cancer mortality • SMHS: highest quintile: HR 0.97 (95% CI 0.81 to 1.13) • SWHS: highest quintile: HR 0.90 (95% CI 0.77 to 1.05)
Selenium levels in exposure categories	SMHS: • Lowest quintile: < 19.36 µg/1000 kcal/d

Sun 2016 *(Continued)*

	• Highest quintile: ≥ 31.92 µg/1000 kcal/d SWHS: • Lowest quintile: < 19.05 µg/1000 kcal/d • Highest quintile: ≥ 33.36 µg/1000 kcal/d
Notes	

Thomson 2008

Methods	Cohort study *Country:* United States
Participants	*Participants:* 133,614 women *Inclusion criteria:* postmenopausal participants (aged 50 to 79 years) of the WHI clinical trial and observational study *Name of parent cohort:* Women's Health Initiative (WHI) *Recruitment*: n.r. *Outcome assessment*: December 2004 *Number of cases:* • Ovarian cancer: 451 *Case definition:* incidence *Years of follow-up:* mean: 7 *Type of selenium marker:* supplemental selenium intake
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox logistical regression *Variables controlled in analysis:* participation in observational or intervention study, age, log calories, number of relatives with breast/ovarian cancer, dietary modification randomisation arm, hysterectomy, minority race, pack-years of smoking, physical activity, NSAID use, parity, infertility, duration of oral contraceptive use, number of lifetime ovulatory cycles, partial oophorectomy, age at menopause, hormone therapy at study entry
Risk estimates [95% CI]	*Reference category:* no intake of supplemental selenium (lowest exposure category) *Results:* Ovarian cancer • Highest exposure category: HR 1.00 (95% CI 0.73 to 1.37)
Selenium levels in exposure categories	Lowest exposure category: no supplemental selenium intake Highest exposure category: > 20 µg/d supplemental selenium intake
Notes	

van den Brandt 1993

Methods	Cohort/subcohort controlled cohort study

van den Brandt 1993 *(Continued)*

	Country: the Netherlands
Participants	*Name of parent cohort:* Netherlands Cohort Study (NLCS) *Recruitment*: 1986 *Case definition:* incidence van den Brandt 1993b *Participants:* 120,852: 58,279 men and 62,573 women; aged 55 to 69 years; returned baseline questionnaire; no history of cancer at baseline *Outcome assessment*: n.r. *Number of cases:* • Stomach cancer: 104 (male/female: 84/20) • Colon cancer: 234 (male/female: 121/113) • Rectal cancer: 113 (male/female: 77/36) van den Brandt 1993a *Participants:* 120,852: 58,279 men and 62,573 women; age 55 to 69 years; returned baseline questionnaire; no history of cancer at baseline *Outcome assessment*: n.r. *Number of cases:* • Lung cancer: 370 (male/female: 335/35) van den Brandt 1994 *Participants:* 62,573 postmenopausal women *Outcome assessment*: 1989 *Number of cases:* • Breast cancer (postmenopausal): 355 (male/female: 0/355) • Breast cancer (postmenopausal), multi-variate analysis: 270 (male/female: 0/270) Zeegers 2002 *Participants:* 120,852: 58,279 men and 62,573 women *Outcome assessment*: December 1992 *Number of cases:* • Bladder cancer: 431 (male/female: 372/59) van den Brandt 2003 *Participants:* 58,279 men *Outcome assessment*: n.r. (probably December 1992) *Number of cases:* • Prostate cancer: 540 (male/female: 540/0) *Years of follow-up:* • 3.3 (Brandt 1993a; Brandt 1993b; Brandt 1994) • 6.3 (Zeegers 2002; Brandt 2003) *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	van den Brandt 1993b *Analysed cases:* 234 of 351 colon cancer cases/104 of 176 stomach cancer cases/113 of 185 rectal cancer cases analysed (reasons for non-inclusion: history of cancer at baseline not available, no pathological confirmation or CIS, no toenail clipping available) *Statistical methods:* Mantel-Haenszel *Variables controlled in analysis:* age, gender van den Brandt 1993a

van den Brandt 1993 *(Continued)*

Analysed cases: 370 of 617 (reasons for non-inclusion: history of cancer at baseline not available, no toenail clipping, no pathological confirmation, problems with selenium measurement)
Statistical methods: Mantel-Haenszel
Variables controlled in analysis: age, gender

van den Brandt 1994
Analysed cases: 355 of 553 (reasons for non-inclusion: history of cancer at baseline not available, CIS, no toenail sample or problems with selenium detection)
Statistical methods: multi-variate case-cohort analysis
Variables controlled in analysis: age, history of benign breast disease, maternal breast cancer, breast cancer in sister(s), age at menarche, age at menopause, oral contraceptive use, parity, age at first birth, body mass index, education, current cigarette smoking, alcohol intake, energy intake

Zeegers 2002
Analysed cases: 431 of 619 (reason for non-inclusion: no toenails available)
Statistical methods: exponentially distributed failure time regression models
Variables controlled in analysis: age, gender, number of cigarettes/d, years of cigarette smoking

van den Brandt 2003
Analysed cases: 540 of 704 (reason for non-inclusion: no toenail samples or selenium detection not possible)
Statistical methods: exponentially distributed failure time regression models
Variables controlled in analysis: age, family history of prostate cancer, number of cigarettes/d, years of cigarette smoking, level of education

Risk estimates [95% CI]

Reference category: lowest quartile/quintile

Results:

van den Brandt 1993b
Stomach cancer
• Both genders: highest quintile: RR 0.61 (95% CI 0.33 to 1.11); highest quintile: RR 0.64 (95% CI 0.33 to 1.27) (max. adj.)
• Men: highest quintile: RR 0.40 (95% CI 0.17 to 0.96) (max. adj.)
• Women: highest quartile: RR 1.68 (95% CI 0.43 to 6.54) (max. adj.)
Colon cancer
• Both genders: highest quintile: RR 0.77 (95% CI 0.49 to 1.19); highest quintile: RR 0.80 (95% CI 0.50 to 1.29) (max. adj.)
• Men: highest quintile: RR 0.82 (95% CI 0.43 to 1.58) (max. adj.)
• Women: highest quintile: RR 0.77 (95% CI 0.41 to 1.45) (max. adj.)
Rectal cancer
• Both genders: highest quintile: RR 1.01 (95% CI 0.55 to 1.84); highest quintile: RR 1.05 (95% CI 0.54 to 2.03) (max. adj.)
• Men: highest quintile: RR 0.91 (95% CI 0.41 to 2.00) (max. adj.)
• Women: highest quartile: RR 1.58 (95% CI 0.59 to 4.22) (max. adj.)

van den Brandt 1993a
Lung cancer
• Both genders: highest quintile: RR 0.40 (95% CI 0.27 to 0.59)
• Men: highest quintile: RR 0.50 (95% CI 0.30 to 0.82)
• Women: highest quartile: RR 0.40 (95% CI 0.13 to 1.24)

van den Brandt 1994
Breast cancer
• Multi-variate analysis: highest quintile: RR 0.84 (95% CI 0.55 to 1.27)
• Age-stratified analysis: highest quintile: RR 0.93 (95% CI 0.65 to 1.33)

Zeegers 2002
Bladder cancer
• Both genders: highest quintile: RR 0.67 (95% CI 0.46 to 0.97)

van den Brandt 2003

van den Brandt 1993 *(Continued)*

	Prostate cancer • Highest quintile: RR 0.69 (95% CI 0.48 to 0.99)
Selenium levels in exposure categories	van den Brandt 1993b • Lowest quintile: ≤ 0.483 µg/g • Highest quintile: ≥ 0.631 µg/g • Lowest quartile: ≤ 0.497 µg/g • Highest quartile: ≥ 0.613 µg/g van den Brandt 1993a *Both genders and men* • Lowest quintile: ≤ 0.483 µg/g • Highest quintile: ≥ 0.631 µg/g *Women* • Lowest quartile ≤ 0.497 µg/g • Highest quartile ≥ 0.613 µg/g van den Brandt 1994 *Women* • Lowest quintile: ≤ 0.499 µg/g • Highest quintile: ≥ 0.646 µg/g Zeegers 2002 • Lowest quintile: ≤ 0.483 µg/g • Highest quintile: ≥ 0.631 µg/g van den Brandt 2003 *Men* • Lowest quintile: ≤ 0.467 µg/g • Highest quintile: ≥ 0.617 µg/g
Notes	*Primary publication:* van den Brandt 1993b *Other publications:* Zeegers 2002, van den Brandt 1993a, van den Brandt 1994, van den Brandt 2003

van Noord 1987

Methods	Matched, nested case-control study *Country:* the Netherlands
Participants	*Participants:* 8760 women *Inclusion criteria:* 42 to 52 years of age; premenopausal; inhabitants of Utrecht *Name of parent cohort:* DOM (Diagnostic onderzoek mammacarcinoom) Study *Recruitment*: n.r. *Outcome assessment*: 1 February 1986 *Number of cases:* • Breast cancer (premenopausal): 27 (male/female: 0/27) *Case definition:* incidence *Years of follow-up:* 0.6 to 3.5, mean: 2.1 *Type of selenium marker:* toenail
Interventions	d.n.a.

van Noord 1987 *(Continued)*

Outcomes	*Analysed cases:* 7 detected during initial mammography screening in this study and not included in the analysis of incident cases *Statistical methods:* n.r. *Variables controlled by matching:* age, date of birth, premenopausal status
Risk estimates [95% CI]	*Reference category:* lowest quartile *Results:* Breast cancer (premenopausal) • Highest quartile: OR 1.1 (95% CI 0.5 to 2.9)
Selenium levels in exposure categories	n.r.
Notes	

Virtamo 1987

Methods	Cohort/subcohort controlled cohort study *Country:* Finland
Participants	*Participants:* 1110 men *Inclusion criteria:* 55 to 74 years of age; inhabitants of Finnish rural areas; participants of prior study on CHD; serum sample available: cases within first year of follow-up excluded *Name of parent cohort:* Men in rural East and West Finland *Recruitment*: 1974 *Outcome assessment*: 31 December 1983 *Number of cases:* • Any cancer: 109 (male/female: 109/0) *Case definition:* incidence *Years of follow-up:* 10 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* conditional logistical regression *Variables controlled in analysis:* age, area of residence, smoking, serum cholesterol, alcohol intake
Risk estimates [95% CI]	*Reference category:* highest tertile *Results:* Any cancer • Lowest tertile OR 1.14 (95% CI 0.66 to 1.98)
Selenium levels in exposure categories	Lowest tertile: 15 to 46 µg/L Highest tertile: 60 to 136 µg/L
Notes	

Walter 2011

Methods	Cohort study *Country:* United States
Participants	*Inclusion criteria:* aged 50 to 76 years, recruited from subscribers to commercial mailing list, residents of western Washington state, non-whites excluded, no malignant disease at baseline *Name of parent cohort:* Vitamins and Lifestyle (VITAL) study *Number of participants:* 66,227 men and women (male/female: n.r.) *Recruitment:* 1 October 2000 to 31 December 2002 *Outcome assessment:* 31/12/2008 *Number of cases:* • Haematological malignancies: 588 *Case definition:* incidence *Years of follow-up:* mean: 6.5 years *Type of selenium marker:* supplemental intake (questionnaire: use of supplements over past 10 years, mean supplemental intake/d calculated)
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox proportional hazard regression *Variables controlled in analysis:* sex, race/ethnicity (white, Hispanic, other), education (high school graduate or less, some college, college or advanced degree), smoking (pack-years), self-rated health (excellent, very good, good, fair, poor), vegetable servings per day (excluding potato servings); fruit servings per day; history of coronary artery disease (defined as history of heart attack, coronary bypass surgery, angioplasty, and/or angina; yes, no), history of rheumatoid arthritis (yes, no), history of fatigue or lack of energy over the year before baseline (yes, no), and number of first-degree relatives with a history of leukaemia or lymphoma (none, 1, 2)
Risk estimates [95% CI]	*Reference category:* none *Results:* Highest level: RR 0.95 (95% CI 0.75 to 1.20)
Selenium levels in exposure categories	Lowest level: none Highest level: 20.1 to 400.0 µg/d
Notes	

Wei 2004

Methods	Frequency-matched cohort-controlled study *Country:* China
Participants	*Participants:* Mark 2000: 29,584 men and women; Wei 2004: 1103 people who were originally selected as disease-free controls in Mark 2000 *Inclusion criteria:* 40 to 69 years of age; healthy inhabitants of 4 Linxian communities; participants of a randomised controlled trial *Name of parent cohort:* General Population Trial Linxian

Wei 2004 *(Continued)*

	Recruitment: 1985 *Outcome assessment:* May 1991 (Mark 2000); n.r. (Wei 2004) *Number of cases:* Wei 2004 • Oesophageal cancer: 75 (male/female: 49/26) mortality • Stomach, cardia cancer: 36 (male/female: 22/14) mortality • Stomach, non-cardia cancer: 24 (male/female: 20/4) mortality • Other: 32 (male/female: 22/10) mortality Mark 2000 • Oesophageal cancer: 590 (male/female: 286/304) incidence • Oesophageal cancer: 332 (male/female: n.r.) mortality • Stomach, cardia cancer: 402 (male/female: 239/163) incidence • Stomach, cardia cancer: 232 (male/female: n.r.) mortality • Stomach, non-cardia cancer: 87 (male/female: 66/21) incidence • Stomach, non-cardia cancer: 68 (male/female: n.r.) mortality *Case definition:* mortality, incidence *Years of follow-up:* unclear/approximately 9 (Wei 2004), 6 (Mark 2000) *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* Cox-proportional hazard model *Variables controlled in analysis:* Wei 2004: age, cholesterol, smoking, alcohol intake, BMI; Mark 2000: age *Variables controlled by matching:* age category, gender
Risk estimates [95% CI]	Wei 2004 *Reference category:* lowest quartile *Results:* Oesophageal cancer • Both genders: highest quartile: RR 0.35 (95% CI 0.16 to 0.81) Stomach, cardia cancer • Both genders: highest quartile: RR 0.31 (95% CI 0.11 to 0.87) Stomach, non-cardia cancer • Both genders: highest quartile: RR 1.64 (95% CI 0.49 to 5.48) Other cancers • Both genders: highest quartile: RR 1.95 (95% CI 0.66 to 5.81) Mark 2000 *Reference category:* lowest quartile *Results:* Oesophageal cancer • Both genders/incidence: highest quartile: RR 0.56 (95% CI 0.44 to 0.71) • Both genders/mortality: highest quartile: RR 0.62 (95% CI 0.44 to 0.89) Stomach, cardia cancer • Both genders/incidence: highest quartile: RR 0.47 (95% CI 0.33 to 0.65) • Both genders/mortality: highest quartile: RR 0.59 (95% CI 0.39 to 0.90) Stomach, non-cardia cancer • Both genders/incidence: highest quartile: OR 1.07 (95% CI 0.55 to 2.08) • Both genders/mortality: highest quartile: OR 1.03 (95% CI 0.85 to 2.02)
Selenium levels in exposure categories	Wei 2004 • Lowest quartile: 0.0 to 60.0 µg/L • Highest quartile ≥ 84.5 µg/L

Wei 2004 *(Continued)*

	Mark 2000 • Lowest quartile: 0.00 to 59.70 µg/L • Highest quartile ≥ 82.20 µg/L
Notes	*Primary publication:* Wei 2004 *Other publication:* Mark 2000 Remark: Wei 2004 measured serum selenium in a subcohort derived from 29,584 male and female participants of the Linxian Population Trial. The earlier publication of this study, Mark 2000, reported 332 fatal cases and 590 incident cases. The later publication, Wei 2004, reported deaths from oesophageal cancer among disease-free controls in Mark 2000 and analysed 75 fatal cases.

Willett 1983

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 10,940 men and women *Inclusion criteria:* 30 to 69 years of age; serum sample available (only 4480 samples of cohort were available because of freezer breakdown); participants of an RCT on hypertension; institutionalised and bedfast people excluded *Name of parent cohort:* Hypertension Detection Follow-Up Programme (HDFP) *Recruitment*: 1973 to 1974 *Outcome assessment*: n.r. *Number of cases:* • Any cancer: 111 (male/female: 60/51) *Case definition:* incidence *Years of follow-up:* 5 *Type of selenium marker:* serum
Interventions	d.n.a.
Outcomes	*Statistical methods:* logistical regression of unmatched data *Variables controlled by matching:* age, gender, race/ethnicity, smoking status, year/month of sample collection, initial blood pressure, use of antihypertensive medication, randomisation group • In women: parity, menopausal status
Risk estimates [95% CI]	*Reference category:* highest quintile, highest 3 quintiles *Results:* Any cancer • Both genders: lowest quintile vs highest quintile: OR 2.0 (CI not reported) • Both genders: lowest quintile vs highest 3 quintiles: OR 1.9 (95% CI 1.1 to 3.3)
Selenium levels in exposure categories	Lowest quintile: ≤ 114 µg/L Highest quintile: ≥ 154 µg/L
Notes	

Yoshizawa 1998

Methods	Matched, nested case-control study *Country:* United States
Participants	*Participants:* 33,737 men *Inclusion criteria:* 40 to 75 years of age; physicians from all 50 US states; provision of toenails in 1987 and completed baseline questionnaire in 1986; exclusion of histologically confirmed prostate cancer at baseline, and cases within first 2 years of follow-up *Name of parent cohort:* Health Professionals Follow-Up Study (HPFS) *Recruitment*: 1986 to 1987 *Outcome assessment*: 1994 *Number of cases:* • Prostate cancer: 181 (male/female: 181/0) *Case definition:* incidence *Years of follow-up:* 8 to 9 *Type of selenium marker:* toenail
Interventions	d.n.a.
Outcomes	*Statistical methods:* logistical regression, conditional logistical regression *Variables controlled in analysis:* quintiles of lycopene, saturated fat, calcium, family history of prostate cancer, BMI, vasectomy *Variables controlled by matching:* age, smoking status, year/month of sample collection
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Prostate cancer (advanced) • Highest quintile: OR 0.39 (95% CI 0.18 to 0.84)
Selenium levels in exposure categories	Lowest quintile: 0.530 to 0.730 µg/g Highest quintile: 0.941 to 7.090 µg/g
Notes	

Yu 1991

Methods	Randomised controlled trial *Allocation:* random *Sequence generation:* unclear, not described *Concealment:* unclear, not described *Blinding:* described as double-blind; *blinding of participants:* adequate, placebo tablets; *blinding of investigators and doctors:* unclear *Dropouts/withdrawals:* unclear, not described *Intention-to-treat-analysis:* unclear, not described *Recruitment period:* unclear, not described

Yu 1991 *(Continued)*

	Observation period: 2 years *Study period:* 2 years *Detection of cases:* unclear, use of "national standards" for the diagnosis of liver cancer *Informed consent:* unclear, not described
Participants	*Country:* China *Number of participants:* 2474 *Condition:* first-degree relatives within 3 generations of families with 2 or more cases of liver cancer during the period 1972 to 1985 *Demographics:* gender distribution not reported; age: 15 to 75 years *Recruitment and setting:* Participants were residents in Qidong province.
Interventions	*Intervention:* 200 µg selenium as selenised yeast p.o. daily, intervention period unclear *Control:* placebo
Outcomes	*Primary outcome measure:* incidence of primary liver cancer within 2 years after start of intervention *Results:* • 13 cases in 1030 placebo participants • 10 cases in 1444 selenium participants
Risk estimates [95% CI]	n.r.
Selenium levels in exposure categories	d.n.a.
Notes	Data were extracted from Yu 1991. We identified 2 later publications (Li 1992, Yu 1993), which we assumed to report on the same trial as Yu 1991. However, the total number of participants differed from the initial report (N = 3849 in the later publications, with 1485 receiving placebo and 2364 receiving selenium). The total number of cases was not reported in either Li 1992 or Yu 1993. Reported results were as follows: Li 1992 *Person-year incidence rate in intervention and control groups*: • Within 1 year of follow-up: selenium group 175.36/100,000; placebo group: 414.65/100,000 • Within 2 years of follow-up: selenium group 219.37/100,000; placebo group: 553.15/100,000 Yu 1993 *Cumulated incidence* • After 1 year: selenium group 1.75/1000; placebo group: 4.15/1000 • After 2 years: selenium group 2.19/1000; placebo group: 5.53/1000 • We could not make contact with study investigators to clarify these discrepancies. As we could not clarify the actual number of liver cancer cases in the later publications, we decided to use the data of Yu 1991 for this review.

Yu 1991 *(Continued)*

• Adverse effects were not mentioned in Yu 1991 or Li 1992. Yu 1993 stated that no cases of selenosis were observed in the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants blinded, doctors stated only as double-blind
Selective reporting (reporting bias)	Unclear risk	Recruitment period unclear; dropout unclear

Yu 1997

Methods	Randomised controlled trial *Allocation:* random *Sequence generation:* unclear, not described *Concealment:* unclear, not described *Blinding: of participants:* adequate (placebo); *of investigators and doctors:* unclear, not described *Dropouts/withdrawals:* unclear, not described *Recruitment period:* unclear, not described *Intention-to-treat-analysis:* unclear, not described *Observation period:* 1987 to 1994 *Intervention period:* 1987 to 1990 *Detection of cases:* unclear, monthly blood sample during follow-up for liver enzymes (SGPT, ZnTT), use of "national standards" for the diagnosis of liver cancer *Informed consent:* unclear, not described
Participants	*Country:* China *Number of participants:* 226 (selenium group: 113; placebo group 113) *Condition:* HBs-antigen carriers with normal liver function *Demographics:* 95 men, 131 women; age: 21 to 63 years *Recruitment and setting:* recruitment “through screening in a village in the city Qidong” (Li 1992)
Interventions	*Intervention:* 200 µg selenium as selenised yeast p.o. daily for 4 years *Control:* placebo

Yu 1997 *(Continued)*

Outcomes	*Primary outcome measure:* incidence of primary liver cancer (defined as increase in SGPT and ZnTT) *Results:* At end of intervention period • 0 cases in the selenium group • 7 cases in the placebo group for a total of 445 person-years of observation (person-time incidence rate: 1573.03/100,000)
Risk estimates [95% CI]	n.r.
Selenium levels in exposure categories	d.n.a.
Notes	*Adverse effects:* "No side effects have been found in these trials" (Yu 1997, p. 124) *Further data reported in:* Li 1992 (Chinese, translated); Yu 1991 In Yu 1991, a different incidence was reported for the selenium group (5 cases). We could not clarify this discrepancy with later papers Li 1992 and Yu 1997.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants blinded, doctors stated only as double-blind
Selective reporting (reporting bias)	Unclear risk	Recruitment period unclear; dropout unclear

Yu 1999

Methods	Matched, nested case-control study *Country:* China (Taiwan)
Participants	*Participants:* 4841 men *Inclusion criteria:* 30 to 65 years of age; HBs-Ag-positive or/and HCV-positive; recruited at 2 centres: Government Employee Central Clinics and Liver Unit of Chang-Gung Memorial Hospital *Recruitment:* August 1988 to June 1992 *Outcome assessment:* 31 December 1996 *Number of cases:* • Primary liver cancer: 69 (male/female: 69/0) *Case definition:* incidence *Years of follow-up:* 4.5 to 8.3

Yu 1999 *(Continued)*

	Type of selenium marker: plasma
Interventions	d.n.a.
Outcomes	*Analysed cases:* 69 of 73 (reason for non-inclusion: no sample available) *Statistical methods:* conditional logistical regression *Variables controlled in analysis:* age, cigarette smoking, alcohol intake, plasma levels of retinol/alpha-tocopherol/alpha-carotene/beta-carotene/lycopene *Variables controlled by matching:* age, year and season of sample collection, recruitment clinic
Risk estimates [95% CI]	*Reference category:* lowest quintile *Results:* Primary liver cancer • Highest quintile: OR 0.62 (95% CI 0.21 to 1.86)
Selenium levels in exposure categories	Lowest quintile ≤ 124.90 µg/L Highest quintile ≥ 162.40 µg/L
Notes	

µ: micro.
AFP: alpha-fetoprotein.
ALT: alanine aminotransferase.
ATBC: alpha-tocopherol, beta-carotene cancer prevention study.
AU: arbitrary unit.
AUA: American Urological Association.
BCC: basal cell carcinoma.
BMI: body mass index.
BPH: benign prostate hyperplasia.
CARET: Carotene and Retinol Efficacy Trial.
CHD: coronary heart disease.
CI: confidence interval.
CIS: carcinoma in situ.
CSDLH: Canadian Study of Diet, Lifestyle and Health.
CT: computed tomography.
CVD: cardiovascular disease.
dL: deciliter.
d.n.a.: does not apply.
DOM: Diagnostic onderzoek mammacarcinoom.
DSMC: Data and Safety Monitoring Committee.
ECOG: Eastern Cooperative Oncology Group.EPIC: European Prospective Investigation of Cancer.EVA: Etude du Vieillissement Antériel.
EPOZ: Epidemiologisch onderzoek naar risico-indicatoren voor hart- en vaatziekten.
FFQ: food-frequency questionnaire.
g: gram.
GBTC: gallbladder and biliary tract cancer.
HBs-Ag: hepatitis B surface antigen.
HCC: hepatocellular carcinoma.
HCV: hepatitis C virus.
HGPIN: high-grade prostatic intraepithelial neoplasia.
HPFP: Hypertension Detection Follow-up Programme.
HPFS: Health Professionals Follow-up Study.
HR: hazard ratio.
HRT: hormone replacement therapy.
IHBC: intrahepatic bile duct cancer.
IRR: incident rate ratio.
IU: international unit.
L: litre.
m: milli.

max. adj.: maximally adjusted.
MHC: Mobile Health Clinic.
n: nano.
NHS: Nurses‘ Health Study.
NLCS: Netherlands Cohort Study.
NMSC: non-melanoma skin cancer.
NPCT: Nutritional Prevention of Cancer Trial.
n.r.: not reported.
NSAID: non-steroidal anti-inflammatory drug.
OR: odds ratio.
p.: page.
p.o.: per os.
ppm: parts per million.
PSA: prostate-specific antigen.
RCT: randomised controlled trial.
RR: risk ratio.
SCC: squamous cell carcinoma.
SD: standard deviation.
SGPT: alanine aminotransferase.
TIA: transient ischaemic attack.
UK: United Kingdom.
USA: United States of America.
VITAL: Vitamins and Lifestyle study.
WHI: Women's Health Initiative.
ZnTT: zinc turbidity test.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albanes 2014	Same results of SELECT 2009, stratified according to tocopherol status
Bates 2011	Results not reported according to inclusion criteria: HR estimated per SD increase of selenium level reported
Bostick 1993	Cohort study: Iowa Women's Health Study cohort Selenium exposure not assessed according to eligibility: only intake of selenium supplements yes/no in questionnaire assessed
Brock 1991	Case-control study with precancerous condition (carcinoma in situ of the cervix)
Chen 1988	Case-control study
Chen 2003	Case-control study
Connelly-Frost 2009	Case-control study
Costello 2001	APPOSE (Australian Prostate Cancer Prevention Trial Using Selenium): Publication describes study design; trial was not started.
Criqui 1991	Population-based, prospective case-control study: Lipid Research Clinic Prevalence and Follow-Up study Results not reported according to inclusion criteria: differences in mean selenium levels reported
Cui 2007	Nested case-control study

Study	Reason for exclusion
	Selenium exposure not assessed according to eligibility: selenium measurement conducted in tissue of benign breast disease
Davies 2002	Nested case-control study: EPIC Norfolk study cohort Results not reported according to inclusion criteria: RR estimate per unit increase in selenium level reported
Epplein 2014	Results not reported according to inclusion criteria: selenium not reported as independent variable - only selenoprotein P
Fleshner 2003	Randomised Study of Vitamin E, Selenium, and Soy Protein Isolate in Patients with High-Grade Prostatic Intraepithelial Neoplasia: Multi-component Intervention
Geybels 2013	Same population as van den Brandt 1993, restricted only to advanced prostate cancer cases
Geybels 2014	Same population as Geybels 2013, stratified according to genetic variation in *SePP1* and *GPX1*
Hagmar 1992	Historical cohort study
Harris 2012	Cancer was not a study endpoint.
Hartman 2002	Nested case-control study: ATBC cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported; OR reported as graph and could not be calculated from reported data
Huzarski 2006	Interventional study without control group with 1489 female participants with *BRCA1* mutation who received a selenium-containing nutritional supplement
Joniau 2007	Intervention study without control group with male participants with high-grade intraepithelial neoplasia of the prostate who received a selenium-containing nutritional supplement
Karunasinghe 2012	Results not reported according to inclusion criteria: differences in mean selenium levels reported
Kellen 2008	Case-control study
Kilander 2001	Cohort study in Uppsala/Sweden Results not reported according to inclusion criteria: RR estimate per unit increase in selenium level reported
Knekt 1988a	Nested case-control study: Mobile Health Clinic cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
Knekt 1988b	Nested case-control study: Mobile Health Clinic cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
Knekt 1991	Nested case-control study: Mobile Health Clinic cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
Kok 1987b	Nested case-control study: Zoetermeer cohort

Study	Reason for exclusion
	Results not reported according to inclusion criteria: differences in mean selenium levels reported
Kune 2006	Case-control study
Kuroda 1988	Case-control study
Lane 2017	Some study participants had cancer at baseline.
Lawson 2007	Cohort study on multi-vitamin use and risk of prostate cancer
Le Marchand 2006	Case-control study
Li 2004b	RCT for gastric cancer prevention with multi-component intervention (200 mg synthetic allitridum and 100 µg selenium per day)
Limburg 2005	Randomised controlled trial: Primary endpoint in this 2-by-2 factorial design trial with selenomethionine 200 µg daily and/or celecoxib 200 mg twice daily was the per-participant change (regression, stable, progression) in pre-existing oesophageal dysplasia - cancer incidence and mortality were not endpoints in this study.
Linxian Pilot 2000	Randomised controlled trial of selenium supplements and celecoxib in participants with oesophageal squamous dysplasia in Linxian, China Endpoint was "regression of disease"; cancer was not an endpoint in this investigation.
Loeb 2015	Selenium exposure not assessed according to eligibility: only intake of selenium supplements yes/no on questionnaire assessed
Martinez 2014	Same participants as SELECT 2009, stratified according to *NKX3.1* genetic variant
Neuhouser 2009	Cohort study (Women's Health Initiative) on multi-vitamin use and risks of cancer and cardiovascular disease No data reported for selenium and cancer risk
Persson 2000	Selenium exposure not assessed according to eligibility
Ray 2006	Cohort study (Women's Health and Aging Studies I and II) on selenium and carotenoid serum levels and mortality No data reported for selenium and cancer mortality
Rayman 2001	PRECISE trial (Prevention of Cancer by Intervention with Selenium): Trial has been stopped.
Rendon	Randomised controlled trial: Vitamin E, Selenium, and Soy Protein in Preventing Cancer in Patients With High-Grade Prostate Neoplasia: Multi-component Intervention
Steevens 2010b	Cancer was not a study endpoint.
Thompson 2009	Cohort study: Iowa Women's Health Study cohort Selenium exposure was not assessed according to eligibility; only intake of selenium supplements yes/no on questionnaire was assessed.
Tsugane 1996	Case-control and cross-sectional studies
Ujiie 2002	Part of this study is a prospective cohort study in Miyagi/Japan.

Study	Reason for exclusion
	Results were not reported according to inclusion criteria; differences in mean selenium levels were reported.
van Noord 1992	Nested case-control study: DOM cohort Results were not reported according to inclusion criteria; differences in mean selenium levels were reported.
van Noord 1993	Nested case-control study: DOM II cohort Results were not reported according to inclusion criteria; RR estimate per unit increase in selenium levels were reported.
van't Veer 1996	Case-control study
Wallace 2009	Case-control study
Watters 2009	Cohort study on smoking and prostate cancer risk. Selenium was not reported as an independent variable.
Wright 2004	Cohort study: ATBC cohort Exposure to antioxidants was assessed via a self-developed index.
You 2005	Randomised controlled trial to test retardation of progression of precancerous gastric lesions among 3400 adults in Shandong, China. Intervention: vitamin C, vitamin E, selenium, garlic preparation Multi-component intervention
Yuan 2006	Nested case-control study: Shanghai cohort study No data reported on selenium and cancer risk
Zeegers 2009	Cohort study on factors influencing recurrence or progression of bladder cancer: West Midlands Bladder Cancer Prognosis Programme

µ: micro.
APPOSE: Australian Prostate Cancer Prevention Trial Using Selenium.
ATBC: alpha-tocopherol, beta-carotene cancer prevention study.
BRCA: breast cancer.
DOM: Diagnostic Onderzoek Mammacarcinoom.
EPIC: European Prospective Investigation of Cancer.
m: milli.
g: gram.
OR: odds ratio.
PRECISE: Prevention of Cancer by Intervention with Selenium.
RCT: randomised controlled trial.
SELECT: Selenium and Vitamin E Cancer Prevention Trial.

Characteristics of ongoing studies *[ordered by study ID]*

Argos 2013

Trial name or title	Bangladesh Vitamin E and Selenium Trial (BEST)
Methods	Double-blind, placebo-controlled, 2-by-2 factorial, randomised controlled trial

Argos 2013 *(Continued)*

Participants	7000 adults having manifest arsenical skin lesions in Bangladesh *Inclusion* • Manifest arsenical skin lesions • Aged 25 to 65 years • Signed informed consent *Exclusion* • Currently pregnant • Not a permanent resident of study area • Unwillingness to discontinue current vitamin use • History of cancer • Too ill to participate • Unwillingness to provide biological samples (blood and urine)
Interventions	6-year supplementation, divided into 4 study arms: • Vitamin E (alpha-tocopherol, 100 mg daily) • Selenium (L-selenomethionine, 200 µg daily) • Vitamin E and selenium • Placebo
Outcomes	*Primary endpoints* • Prevention of non-melanoma skin cancer *Secondary endpoints:* • All-cause and cancer mortality • Diabetes mellitus • Oxidative stress biomarkers
Starting date	April 2006
Contact information	Dr. Habibul Ahsan Center for Cancer Epidemiology and Prevention, The University of Chicago 5841 South Maryland Avenue, MC 2007 Chicago, IL 60637
Notes	

BEST: Bangladesh Vitamin E and Selenium Trial.

DATA AND ANALYSES

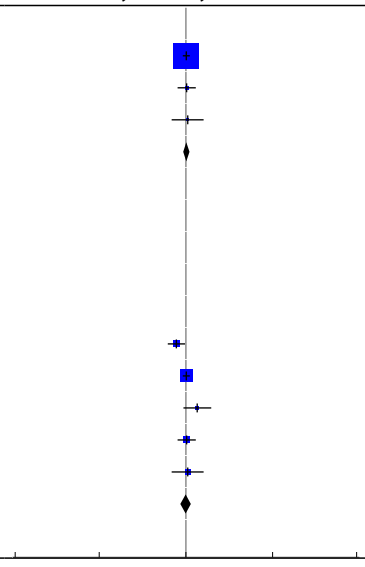
Comparison 1. Randomised controlled trials: highest versus lowest selenium exposure

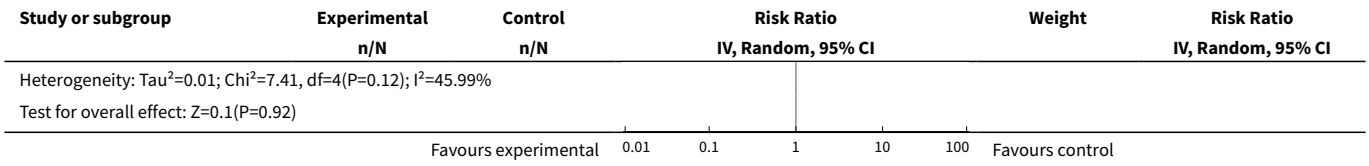
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Any cancer risk	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Studies with low RoB	3	19475	Risk Ratio (IV, Random, 95% CI)	1.01 [0.93, 1.10]
1.2 All studies	5	21860	Risk Ratio (IV, Random, 95% CI)	0.99 [0.86, 1.14]
2 Cancer mortality	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 Studies with low RoB	1	17448	Risk Ratio (IV, Random, 95% CI)	1.02 [0.80, 1.30]
2.2 All studies	2	18698	Risk Ratio (IV, Random, 95% CI)	0.81 [0.49, 1.32]
3 Head and neck cancer risk	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Studies with low RoB	1	1561	Risk Ratio (IV, Random, 95% CI)	1.00 [0.18, 5.45]
3.2 All studies	2	2811	Risk Ratio (IV, Random, 95% CI)	1.22 [0.52, 2.85]
4 Oesophageal cancer risk	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Studies with low RoB	1	1561	Risk Ratio (IV, Random, 95% CI)	1.50 [0.06, 36.86]
4.2 All studies	2	2811	Risk Ratio (IV, Random, 95% CI)	0.53 [0.12, 2.28]
5 Colorectal cancer risk	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 Studies with low RoB	2	19009	Risk Ratio (IV, Random, 95% CI)	0.99 [0.69, 1.43]
5.2 All studies	3	20259	Risk Ratio (IV, Random, 95% CI)	0.74 [0.41, 1.33]
6 Liver cancer risk	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.1 Studies with low RoB	1	1561	Risk Ratio (IV, Random, 95% CI)	6.52 [0.37, 115.49]
6.2 All studies	4	6326	Risk Ratio (IV, Random, 95% CI)	0.52 [0.35, 0.79]
7 Melanoma risk	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.1 Studies with low RoB	2	2027	Risk Ratio (IV, Random, 95% CI)	1.35 [0.41, 4.52]
7.2 All studies	3	3277	Risk Ratio (IV, Random, 95% CI)	1.28 [0.63, 2.59]
8 Non-melanoma skin cancer risk	4		Risk Ratio (Random, 95% CI)	Subtotals only
8.1 Studies with low RoB	2	2027	Risk Ratio (Random, 95% CI)	1.16 [0.30, 4.42]
8.2 All studies	4	3461	Risk Ratio (Random, 95% CI)	1.23 [0.73, 2.08]
9 Lung cancer risk	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 Studies with low RoB	2	19009	Risk Ratio (IV, Random, 95% CI)	1.16 [0.89, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 All studies	3	20259	Risk Ratio (IV, Random, 95% CI)	1.03 [0.78, 1.37]
10 Breast cancer risk	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1 Studies with low RoB	1	802	Risk Ratio (IV, Random, 95% CI)	2.04 [0.44, 9.55]
10.2 All studies	3	2260	Risk Ratio (IV, Random, 95% CI)	1.44 [0.96, 2.17]
11 Bladder cancer risk	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.1 Studies with low RoB	2	19009	Risk Ratio (IV, Random, 95% CI)	1.07 [0.76, 1.52]
11.2 All studies	3	20259	Risk Ratio (IV, Random, 95% CI)	1.10 [0.79, 1.52]
12 Prostate cancer risk	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
12.1 Studies with low RoB	4	18942	Risk Ratio (IV, Random, 95% CI)	1.01 [0.90, 1.14]
12.2 All studies	5	19869	Risk Ratio (IV, Random, 95% CI)	0.91 [0.75, 1.12]
13 Leukaemia and lymphoma risk	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
13.1 Studies with low RoB	1	1561	Risk Ratio (IV, Random, 95% CI)	1.00 [0.25, 3.99]
13.2 All studies	2	2811	Risk Ratio (IV, Random, 95% CI)	1.21 [0.52, 2.80]

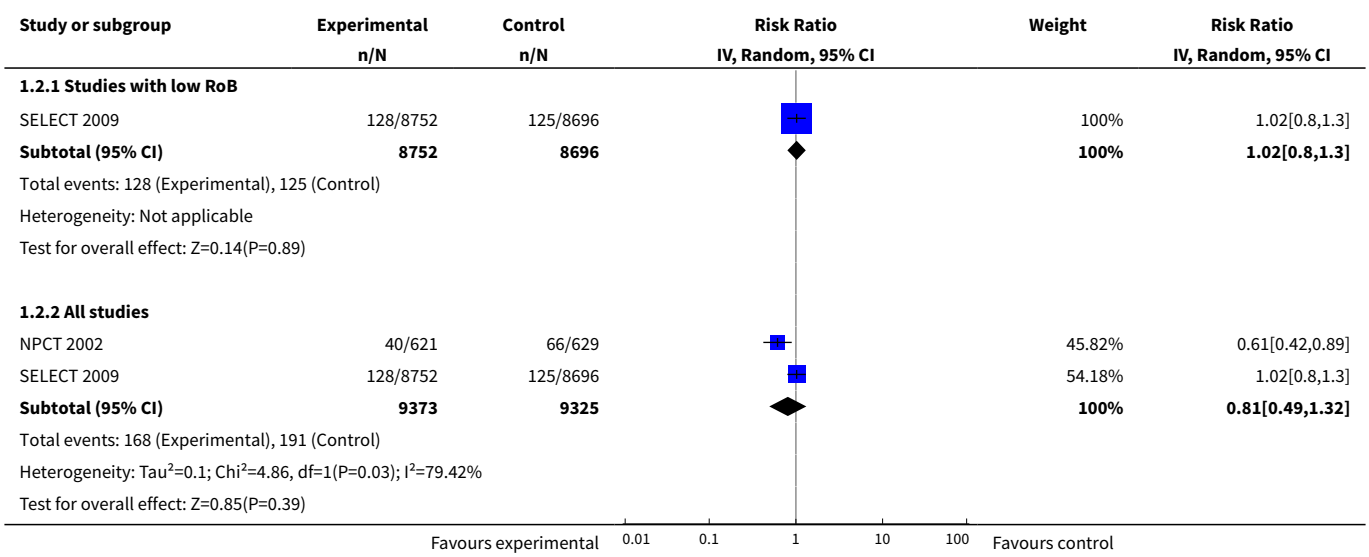
Analysis 1.1. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 1 Any cancer risk.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Studies with low RoB					
SELECT 2009	837/8752	824/8696		83.98%	1.01[0.92,1.11]
Karp 2013	169/1040	83/521		12.13%	1.02[0.8,1.3]
Algotar 2013	37/234	35/232		3.89%	1.05[0.69,1.6]
Subtotal (95% CI)	**10026**	**9449**		**100%**	**1.01[0.93,1.1]**
Total events: 1043 (Experimental), 942 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=0.28(P=0.78)					
1.1.2 All studies					
NPCT 2002	105/621	137/629		21%	0.78[0.62,0.98]
SELECT 2009	837/8752	824/8696		39.06%	1.01[0.92,1.11]
Lubinski 2011	60/563	45/572		11.18%	1.35[0.94,1.96]
Karp 2013	169/1040	83/521		19.83%	1.02[0.8,1.3]
Algotar 2013	37/234	35/232		8.94%	1.05[0.69,1.6]
Subtotal (95% CI)	**11210**	**10650**		**100%**	**0.99[0.86,1.14]**
Total events: 1208 (Experimental), 1124 (Control)					

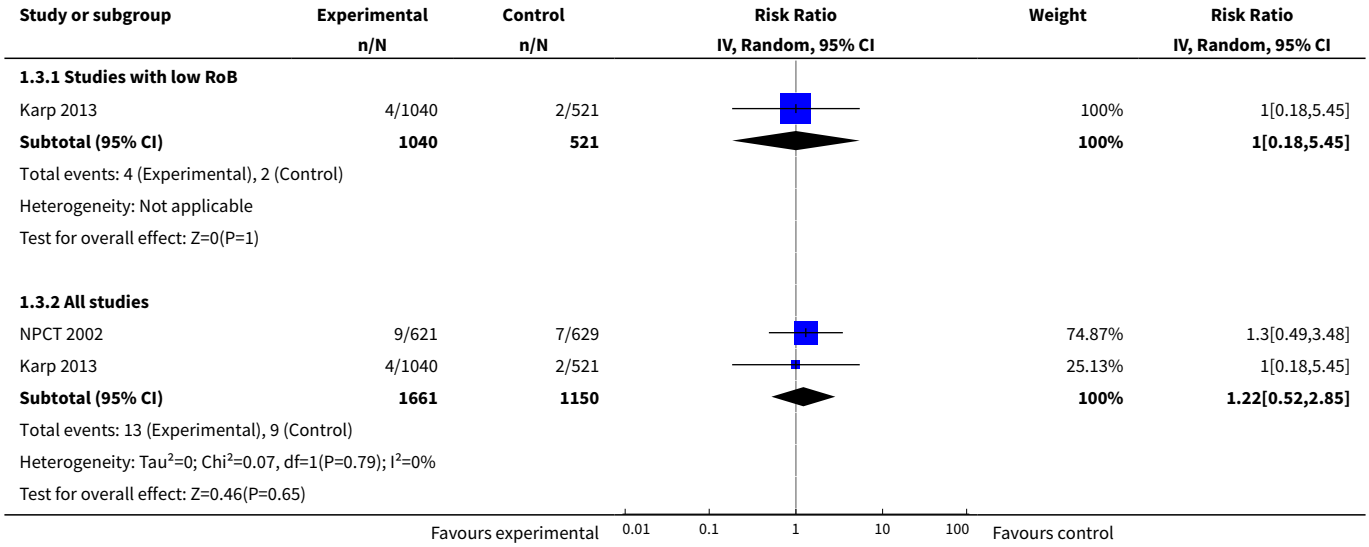




Analysis 1.2. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 2 Cancer mortality.

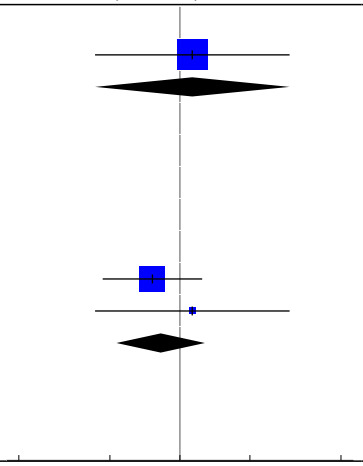


Analysis 1.3. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 3 Head and neck cancer risk.



Analysis 1.4. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 4 Oesophageal cancer risk.

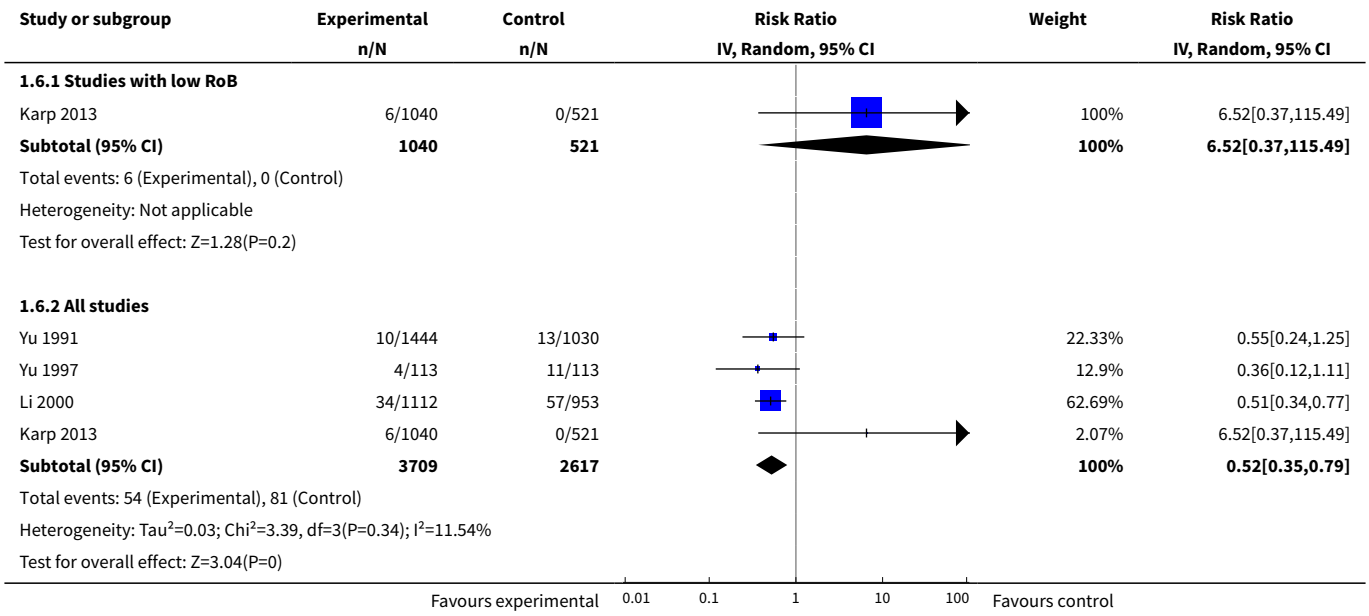
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 Studies with low RoB					
Karp 2013	1/1040	0/521		100%	1.5[0.06,36.86]
Subtotal (95% CI)	**1040**	**521**		**100%**	**1.5[0.06,36.86]**
Total events: 1 (Experimental), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.8)					
1.4.2 All studies					
NPCT 2002	2/621	5/629		79.27%	0.41[0.08,2.08]
Karp 2013	1/1040	0/521		20.73%	1.5[0.06,36.86]
Subtotal (95% CI)	**1661**	**1150**		**100%**	**0.53[0.12,2.28]**
Total events: 3 (Experimental), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.51, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=0.85(P=0.4)					



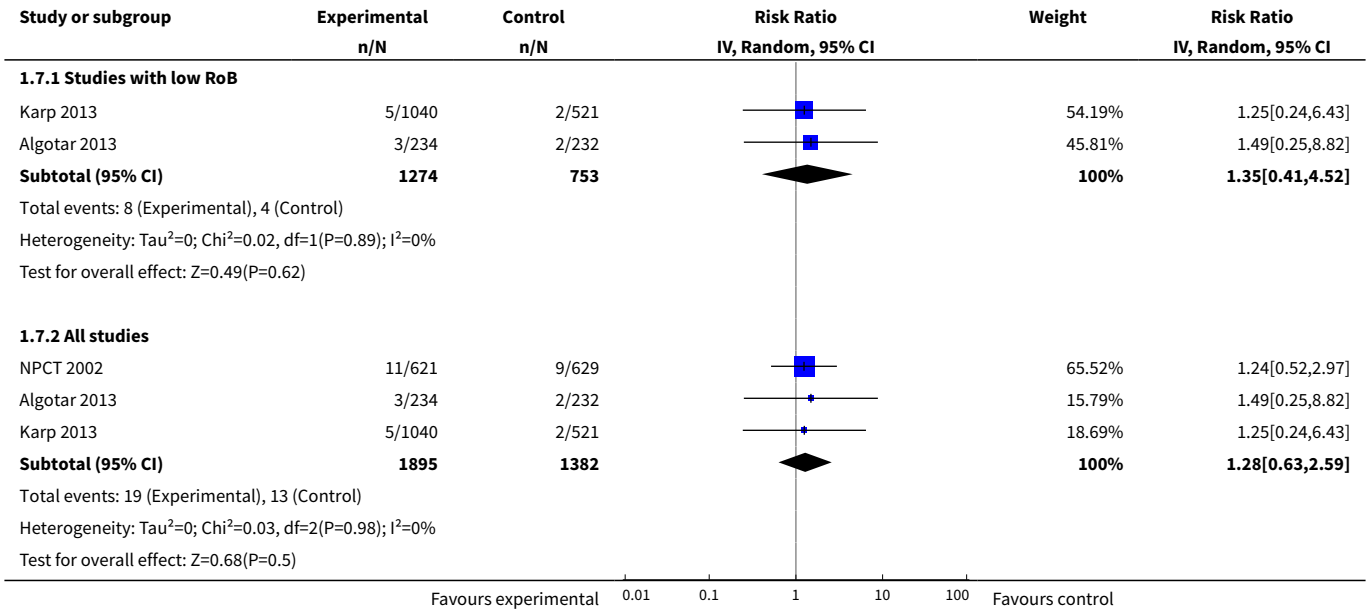
Analysis 1.5. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 5 Colorectal cancer risk.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.5.1 Studies with low RoB					
SELECT 2009	63/8752	60/8696		93.18%	1.04[0.73,1.48]
Karp 2013	4/1040	4/521		6.82%	0.5[0.13,2]
Subtotal (95% CI)	**9792**	**9217**		**100%**	**0.99[0.69,1.43]**
Total events: 67 (Experimental), 64 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.02, df=1(P=0.31); I^2=1.62%					
Test for overall effect: Z=0.04(P=0.97)					
1.5.2 All studies					
NPCT 2002	9/621	19/629		30.87%	0.48[0.22,1.05]
SELECT 2009	63/8752	60/8696		54.74%	1.04[0.73,1.48]
Karp 2013	4/1040	4/521		14.4%	0.5[0.13,2]
Subtotal (95% CI)	**10413**	**9846**		**100%**	**0.74[0.41,1.33]**
Total events: 76 (Experimental), 83 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=3.82, df=2(P=0.15); I^2=47.69%					
Test for overall effect: Z=1.01(P=0.31)					

Analysis 1.6. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 6 Liver cancer risk.



Analysis 1.7. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 7 Melanoma risk.



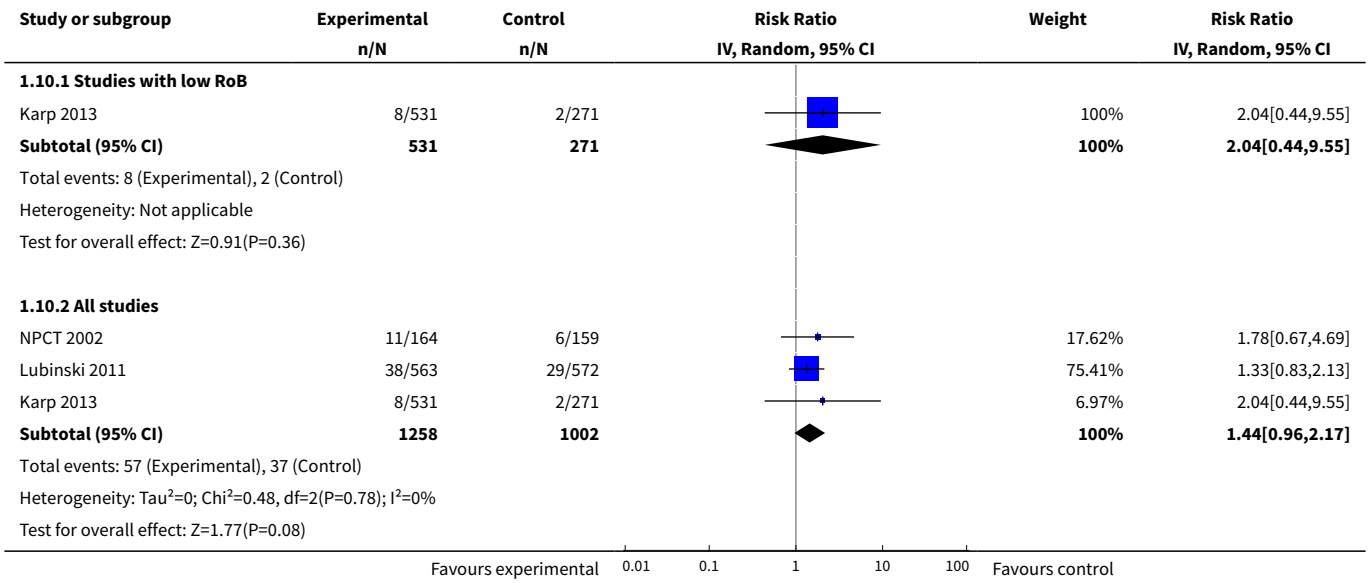
Analysis 1.8. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 8 Non-melanoma skin cancer risk.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.8.1 Studies with low RoB						
Algotar 2013	234	232	1 (0.671)		40.67%	2.64[0.71,9.84]
Karp 2013	1040	521	-0.4 (0.3)		59.33%	0.66[0.37,1.19]
Subtotal (95% CI)					**100%**	**1.16[0.3,4.42]**
Heterogeneity: Tau²=0.69; Chi²=3.58, df=1(P=0.06); I²=72.04%						
Test for overall effect: Z=0.22(P=0.83)						
1.8.2 All studies						
NPCT 2002	621	629	0.2 (0.069)		48.07%	1.27[1.11,1.45]
Dreno 2007	91	93	1.1 (0.803)		9.13%	3.07[0.64,14.8]
Karp 2013	1040	521	-0.4 (0.3)		30.68%	0.66[0.37,1.19]
Algotar 2013	234	232	1 (0.671)		12.12%	2.64[0.71,9.84]
Subtotal (95% CI)					**100%**	**1.23[0.73,2.08]**
Heterogeneity: Tau²=0.15; Chi²=7.11, df=3(P=0.07); I²=57.8%						
Test for overall effect: Z=0.77(P=0.44)						

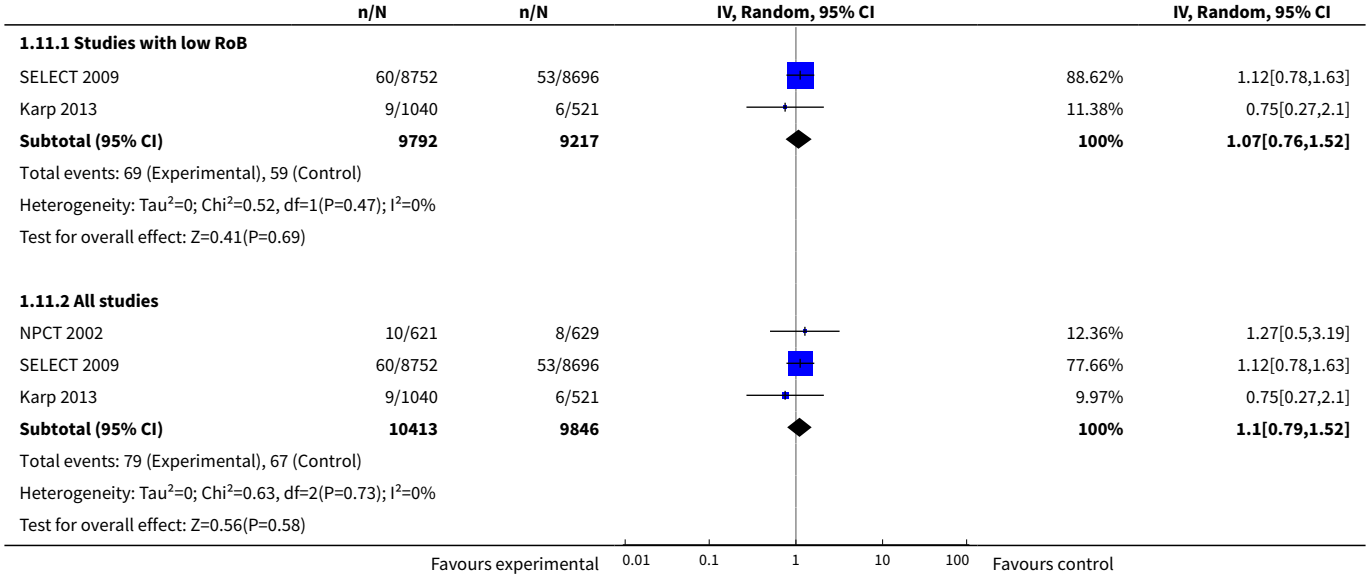
Analysis 1.9. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 9 Lung cancer risk.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.9.1 Studies with low RoB					
SELECT 2009	75/8752	67/8696		62.8%	1.11[0.8,1.54]
Karp 2013	69/1040	28/521		37.2%	1.23[0.81,1.89]
Subtotal (95% CI)	**9792**	**9217**		**100%**	**1.16[0.89,1.5]**
Total events: 144 (Experimental), 95 (Control)					
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.7); I²=0%					
Test for overall effect: Z=1.09(P=0.27)					
1.9.2 All studies					
NPCT 2002	25/621	35/629		24.42%	0.72[0.44,1.19]
SELECT 2009	75/8752	67/8696		44.38%	1.11[0.8,1.54]
Karp 2013	69/1040	28/521		31.2%	1.23[0.81,1.89]
Subtotal (95% CI)	**10413**	**9846**		**100%**	**1.03[0.78,1.37]**
Total events: 169 (Experimental), 130 (Control)					
Heterogeneity: Tau²=0.02; Chi²=2.79, df=2(P=0.25); I²=28.41%					
Test for overall effect: Z=0.24(P=0.81)					

Analysis 1.10. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 10 Breast cancer risk.

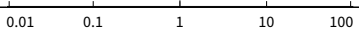


Analysis 1.11. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 11 Bladder cancer risk.



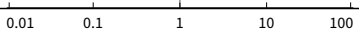
Analysis 1.12. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 12 Prostate cancer risk.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.12.1 Studies with low RoB					
SELECT 2009	432/8752	416/8696		79.38%	1.03[0.9,1.18]
Marshall 2011	48/135	49/134		13.51%	0.97[0.71,1.34]
Karp 2013	16/509	9/250		2.13%	0.87[0.39,1.95]
Algotar 2013	24/234	26/232		4.98%	0.92[0.54,1.55]
Subtotal (95% CI)	**9630**	**9312**		**100%**	**1.01[0.9,1.14]**
Total events: 520 (Experimental), 500 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=3(P=0.94); I^2=0%					
Test for overall effect: Z=0.23(P=0.82)					
1.12.2 All studies					
NPCT 2002	22/457	42/470		12.71%	0.54[0.33,0.89]
SELECT 2009	432/8752	416/8696		46.18%	1.03[0.9,1.18]
Marshall 2011	48/135	49/134		23.64%	0.97[0.71,1.34]
Algotar 2013	24/234	26/232		11.78%	0.92[0.54,1.55]
Karp 2013	16/509	9/250		5.69%	0.87[0.39,1.95]
Subtotal (95% CI)	**10087**	**9782**		**100%**	**0.91[0.75,1.12]**
Total events: 542 (Experimental), 542 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=6.25, df=4(P=0.18); I^2=36.01%					
Test for overall effect: Z=0.86(P=0.39)					



Analysis 1.13. Comparison 1 Randomised controlled trials: highest versus lowest selenium exposure, Outcome 13 Leukaemia and lymphoma risk.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.13.1 Studies with low RoB					
Karp 2013	6/1040	3/521		100%	1[0.25,3.99]
Subtotal (95% CI)	**1040**	**521**		**100%**	**1[0.25,3.99]**
Total events: 6 (Experimental), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0(P=1)					
1.13.2 All studies					
NPCT 2002	8/621	6/629		63.28%	1.35[0.47,3.87]
Karp 2013	6/1040	3/521		36.72%	1[0.25,3.99]
Subtotal (95% CI)	**1661**	**1150**		**100%**	**1.21[0.52,2.8]**
Total events: 14 (Experimental), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%					
Test for overall effect: Z=0.45(P=0.66)					



Comparison 2. Observational studies: highest versus lowest selenium exposure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cancer incidence and mortality	14		Odds Ratio (Random, 95% CI)	Subtotals only
1.1 Incidence	7		Odds Ratio (Random, 95% CI)	0.72 [0.55, 0.93]
1.2 Mortality	7		Odds Ratio (Random, 95% CI)	0.76 [0.59, 0.97]
2 Total cancer incidence and mortality (men)	8		Odds Ratio (Random, 95% CI)	Subtotals only
2.1 Incidence	4		Odds Ratio (Random, 95% CI)	0.72 [0.46, 1.14]
2.2 Mortality	4		Odds Ratio (Random, 95% CI)	0.65 [0.45, 0.94]
3 Total cancer incidence and mortality (women)	6		Odds Ratio (Random, 95% CI)	Subtotals only
3.1 Incidence	2		Odds Ratio (Random, 95% CI)	0.90 [0.45, 1.77]
3.2 Mortality	4		Odds Ratio (Random, 95% CI)	0.91 [0.80, 1.03]
4 Total cancer incidence and mortality (ascending order of selenium levels)	13		Odds Ratio (Random, 95% CI)	Subtotals only
4.1 Incidence	7	1642	Odds Ratio (Random, 95% CI)	0.72 [0.55, 0.93]
4.2 Mortality	6	1230	Odds Ratio (Random, 95% CI)	0.63 [0.39, 1.01]
5 Total cancer incidence and mortality (ascending order of differences in selenium levels)	13		Odds Ratio (Random, 95% CI)	Subtotals only
5.1 Incidence	7	190	Odds Ratio (Random, 95% CI)	0.72 [0.55, 0.93]
5.2 Mortality	6	106	Odds Ratio (Random, 95% CI)	0.63 [0.39, 1.01]
6 Stomach cancer risk	5		Odds Ratio (Random, 95% CI)	0.66 [0.43, 1.01]
7 Stomach cancer risk (by sex)	5		Odds Ratio (Random, 95% CI)	0.66 [0.42, 1.04]

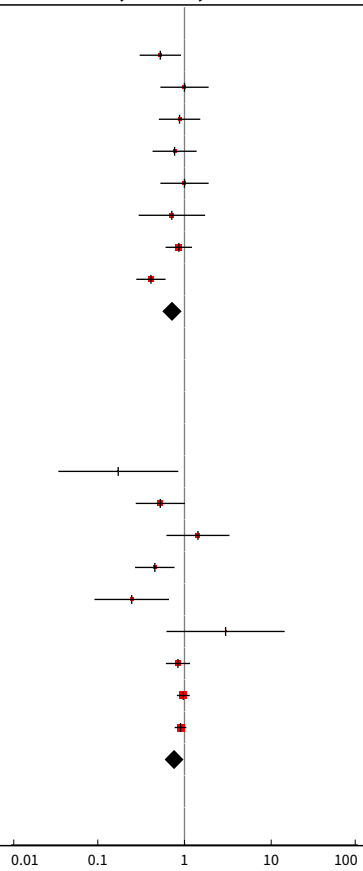
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1 All (male + female)	2		Odds Ratio (Random, 95% CI)	0.75 [0.41, 1.36]
7.2 Male	3		Odds Ratio (Random, 95% CI)	0.43 [0.14, 1.32]
7.3 Female	2		Odds Ratio (Random, 95% CI)	0.73 [0.12, 4.35]
8 Colorectal cancer risk	6		Odds Ratio (Random, 95% CI)	0.82 [0.72, 0.94]
9 Colorectal cancer risk (by sex)	6		Odds Ratio (Random, 95% CI)	0.83 [0.72, 0.95]
9.1 All (male + female)	1		Odds Ratio (Random, 95% CI)	0.80 [0.68, 0.94]
9.2 Male	4		Odds Ratio (Random, 95% CI)	0.86 [0.65, 1.16]
9.3 Female	4		Odds Ratio (Random, 95% CI)	0.96 [0.61, 1.50]
10 Colon cancer risk	5		Odds Ratio (Random, 95% CI)	0.81 [0.69, 0.96]
11 Colon cancer risk (by sex)	5		Odds Ratio (Random, 95% CI)	0.81 [0.69, 0.96]
11.1 All (male + female)	2		Odds Ratio (Random, 95% CI)	0.84 [0.68, 1.03]
11.2 Male	3		Odds Ratio (Random, 95% CI)	0.84 [0.56, 1.25]
11.3 Female	2		Odds Ratio (Random, 95% CI)	0.68 [0.44, 1.04]
12 Lung cancer incidence and mortality	13		Odds Ratio (Random, 95% CI)	Subtotals only
12.1 Incidence	11		Odds Ratio (Random, 95% CI)	0.82 [0.59, 1.14]
12.2 Mortality	2		Odds Ratio (Random, 95% CI)	1.34 [0.93, 1.93]
13 Lung cancer risk (sex-disaggregated data)	13		Odds Ratio (Random, 95% CI)	0.89 [0.69, 1.14]
13.1 All (male + female)	5		Odds Ratio (Random, 95% CI)	0.74 [0.43, 1.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Male	7		Odds Ratio (Random, 95% CI)	0.98 [0.68, 1.39]
13.3 Female	4		Odds Ratio (Random, 95% CI)	0.83 [0.43, 1.61]
14 Lung cancer risk (by exposure assessment)	13		Odds Ratio (Random, 95% CI)	0.88 [0.65, 1.18]
14.1 Intake	2		Odds Ratio (Random, 95% CI)	1.32 [0.95, 1.84]
14.2 Serum or plasma	9		Odds Ratio (Random, 95% CI)	0.91 [0.70, 1.18]
14.3 Toenail	2		Odds Ratio (Random, 95% CI)	1.05 [0.11, 10.36]
15 Lung cancer risk (ascending order of selenium levels)	8	1938	Odds Ratio (Random, 95% CI)	0.97 [0.74, 1.27]
16 Lung cancer risk (ascending order of differences in selenium levels)	8	188	Odds Ratio (Random, 95% CI)	0.97 [0.74, 1.27]
17 Breast cancer risk (women)	8		Odds Ratio (Random, 95% CI)	1.09 [0.87, 1.37]
18 Bladder cancer risk	5		Odds Ratio (Random, 95% CI)	0.67 [0.46, 0.97]
18.1 All (male + female)	2		Odds Ratio (Random, 95% CI)	0.65 [0.46, 0.92]
18.2 Male	3		Odds Ratio (Random, 95% CI)	0.82 [0.41, 1.62]
18.3 Female	1		Odds Ratio (Random, 95% CI)	0.36 [0.14, 0.92]
19 Prostate cancer risk	21		Odds Ratio (Random, 95% CI)	0.84 [0.75, 0.95]
20 Prostate cancer risk (by exposure assessment)	21		Odds Ratio (Random, 95% CI)	0.84 [0.75, 0.95]
20.1 Intake and supplement	4		Odds Ratio (Random, 95% CI)	0.99 [0.85, 1.15]
20.2 Serum or plasma	13		Odds Ratio (Random, 95% CI)	0.86 [0.75, 0.99]
20.3 Toenail	4		Odds Ratio (Random, 95% CI)	0.60 [0.44, 0.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Prostate cancer risk (ascending order of selenium levels)	13	2816	Odds Ratio (Random, 95% CI)	0.86 [0.75, 0.99]
22 Prostate cancer risk (ascending order of differences in selenium levels)	13	345	Odds Ratio (Random, 95% CI)	0.86 [0.75, 0.99]

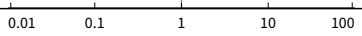
Analysis 2.1. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 1 Total cancer incidence and mortality.

Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.1.1 Incidence						
Willett 1983	0	0	-0.6 (0.28)		12.47%	0.53[0.3,0.91]
Peleg 1985	0	0	0 (0.327)		10.34%	1[0.53,1.9]
Virtamo 1987	0	0	-0.1 (0.28)		12.47%	0.88[0.51,1.52]
Nomura 1987	0	0	-0.3 (0.299)		11.55%	0.77[0.43,1.38]
Coates 1988	0	0	0 (0.327)		10.35%	1[0.53,1.9]
Ringstad 1988	0	0	-0.3 (0.45)		6.56%	0.71[0.3,1.73]
Knekt 1990	0	0	-0.2 (0.179)		18.8%	0.86[0.6,1.22]
Knekt 1990	0	0	-0.9 (0.198)		17.44%	0.41[0.28,0.6]
Subtotal (95% CI)					**100%**	**0.72[0.55,0.93]**
Heterogeneity: Tau^2=0.06; Chi^2=12.75, df=7(P=0.08); I^2=45.11%						
Test for overall effect: Z=2.54(P=0.01)						
2.1.2 Mortality						
Salonen 1985	0	0	-1.8 (0.812)		2.25%	0.17[0.04,0.85]
Kok 1987a	0	0	-0.6 (0.334)		9.21%	0.53[0.27,1.01]
Kornitzer 2004	0	0	0.4 (0.427)		6.58%	1.43[0.62,3.3]
Kornitzer 2004	0	0	-0.8 (0.267)		11.93%	0.45[0.27,0.77]
Akbaraly 2005	0	0	-1.4 (0.505)		5.1%	0.25[0.09,0.66]
Fujishima 2011	0	0	1.1 (0.801)		2.31%	2.98[0.62,14.32]
Goyal 2013	0	0	-0.2 (0.163)		17.68%	0.84[0.61,1.16]
Sun 2016	0	0	-0 (0.087)		22.29%	0.97[0.82,1.15]
Sun 2016	0	0	-0.1 (0.08)		22.66%	0.9[0.77,1.05]
Subtotal (95% CI)					**100%**	**0.76[0.59,0.97]**
Heterogeneity: Tau^2=0.07; Chi^2=23.9, df=8(P=0); I^2=66.53%						
Test for overall effect: Z=2.17(P=0.03)						



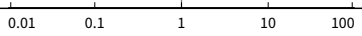
Analysis 2.2. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 2 Total cancer incidence and mortality (men).

Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.2.1 Incidence						
Peleg 1985	0	0	0.5 (0.856)		6.21%	1.67[0.31,8.93]
Peleg 1985	0	0	0.1 (0.496)		14.12%	1.11[0.42,2.94]
Nomura 1987	0	0	-0.3 (0.299)		23.88%	0.77[0.43,1.38]
Virtamo 1987	0	0	-0.1 (0.28)		25.1%	0.88[0.51,1.52]
Knekt 1990	0	0	-0.9 (0.198)		30.68%	0.41[0.28,0.6]
Subtotal (95% CI)					**100%**	**0.72[0.46,1.14]**
Heterogeneity: Tau²=0.14; Chi²=9.12, df=4(P=0.06); I²=56.12%						
Test for overall effect: Z=1.39(P=0.17)						
2.2.2 Mortality						
Kok 1987a	0	0	-1 (0.434)		12.27%	0.37[0.16,0.87]
Kornitzer 2004	0	0	-0.8 (0.267)		20.96%	0.45[0.27,0.77]
Goyal 2013	0	0	-0.4 (0.11)		32.64%	0.67[0.54,0.83]
Sun 2016	0	0	-0 (0.087)		34.12%	0.97[0.82,1.15]
Subtotal (95% CI)					**100%**	**0.65[0.45,0.94]**
Heterogeneity: Tau²=0.09; Chi²=15.16, df=3(P=0); I²=80.21%						
Test for overall effect: Z=2.3(P=0.02)						



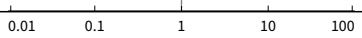
Analysis 2.3. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 3 Total cancer incidence and mortality (women).

Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.3.1 Incidence						
Peleg 1985	0	0	0.5 (0.602)		23.94%	1.67[0.51,5.42]
Peleg 1985	0	0	-1.8 (1.229)		7.32%	0.17[0.02,1.92]
Knekt 1990	0	0	-0.2 (0.179)		68.74%	0.86[0.6,1.22]
Subtotal (95% CI)					**100%**	**0.9[0.45,1.77]**
Heterogeneity: Tau²=0.14; Chi²=2.9, df=2(P=0.23); I²=31.12%						
Test for overall effect: Z=0.32(P=0.75)						
2.3.2 Mortality						
Kok 1987a	0	0	-0.4 (0.527)		1.55%	0.67[0.24,1.87]
Kornitzer 2004	0	0	0.4 (0.427)		2.36%	1.43[0.62,3.3]
Goyal 2013	0	0	-0.1 (0.124)		28.1%	0.91[0.71,1.16]
Sun 2016	0	0	-0.1 (0.08)		67.98%	0.9[0.77,1.05]
Subtotal (95% CI)					**100%**	**0.91[0.8,1.03]**
Heterogeneity: Tau²=0; Chi²=1.48, df=3(P=0.69); I²=0%						
Test for overall effect: Z=1.46(P=0.14)						



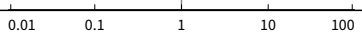
Analysis 2.4. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 4 Total cancer incidence and mortality (ascending order of selenium levels).

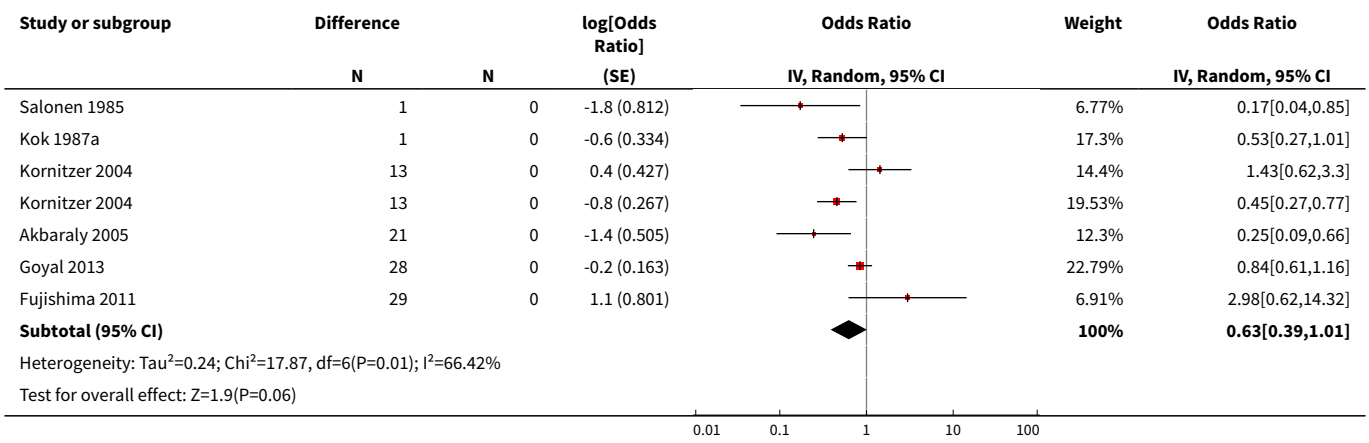
Study or subgroup	Lowest category N	Highest category N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.4.1 Incidence						
Virtamo 1987	46	60	-0.1 (0.28)		12.47%	0.88[0.51,1.52]
Knekt 1990	49	78	-0.9 (0.198)		17.44%	0.41[0.28,0.6]
Knekt 1990	49	78	-0.2 (0.179)		18.8%	0.86[0.6,1.22]
Peleg 1985	103	127	0 (0.327)		10.34%	1[0.53,1.9]
Nomura 1987	103	133	-0.3 (0.299)		11.55%	0.77[0.43,1.38]
Ringstad 1988	114	115	-0.3 (0.45)		6.56%	0.71[0.3,1.73]
Willett 1983	114	154	-0.6 (0.28)		12.47%	0.53[0.3,0.91]
Coates 1988	148	171	0 (0.327)		10.35%	1[0.53,1.9]
Subtotal (95% CI)					**100%**	**0.72[0.55,0.93]**
Heterogeneity: Tau²=0.06; Chi²=12.75, df=7(P=0.08); I²=45.11%						
Test for overall effect: Z=2.54(P=0.01)						
2.4.2 Mortality						
Salonen 1985	47	47	-1.8 (0.812)		6.77%	0.17[0.04,0.85]
Kornitzer 2004	72	85	0.4 (0.427)		14.4%	1.43[0.62,3.3]
Kornitzer 2004	72	85	-0.8 (0.267)		19.53%	0.45[0.27,0.77]
Akbaraly 2005	75	96	-1.4 (0.505)		12.3%	0.25[0.09,0.66]
Fujishima 2011	85	114	1.1 (0.801)		6.91%	2.98[0.62,14.32]
Kok 1987a	103	103	-0.6 (0.334)		17.3%	0.53[0.27,1.01]
Goyal 2013	109	137	-0.2 (0.163)		22.79%	0.84[0.61,1.16]
Subtotal (95% CI)					**100%**	**0.63[0.39,1.01]**
Heterogeneity: Tau²=0.24; Chi²=17.87, df=6(P=0.01); I²=66.42%						
Test for overall effect: Z=1.9(P=0.06)						



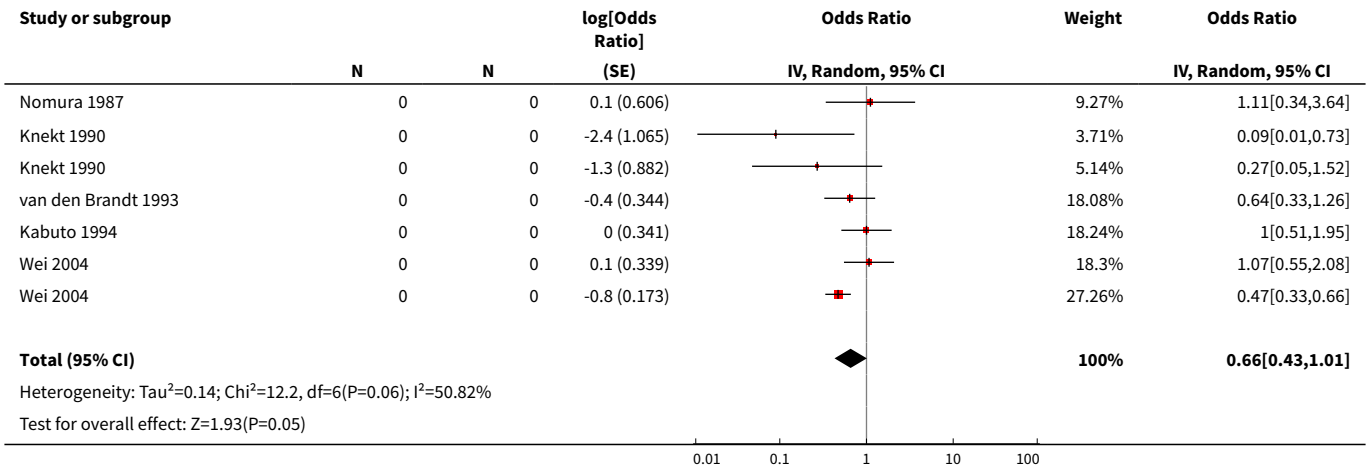
Analysis 2.5. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 5 Total cancer incidence and mortality (ascending order of differences in selenium levels).

Study or subgroup	Difference N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.5.1 Incidence						
Ringstad 1988	1	0	-0.3 (0.45)		6.56%	0.71[0.3,1.73]
Virtamo 1987	14	0	-0.1 (0.28)		12.47%	0.88[0.51,1.52]
Coates 1988	23	0	0 (0.327)		10.35%	1[0.53,1.9]
Peleg 1985	24	0	0 (0.327)		10.34%	1[0.53,1.9]
Knekt 1990	29	0	-0.2 (0.18)		18.8%	0.86[0.6,1.22]
Knekt 1990	29	0	-0.9 (0.198)		17.44%	0.41[0.28,0.6]
Nomura 1987	30	0	-0.3 (0.299)		11.55%	0.77[0.43,1.38]
Willett 1983	40	0	-0.6 (0.28)		12.47%	0.53[0.3,0.91]
Subtotal (95% CI)					**100%**	**0.72[0.55,0.93]**
Heterogeneity: Tau²=0.06; Chi²=12.75, df=7(P=0.08); I²=45.11%						
Test for overall effect: Z=2.54(P=0.01)						
2.5.2 Mortality						

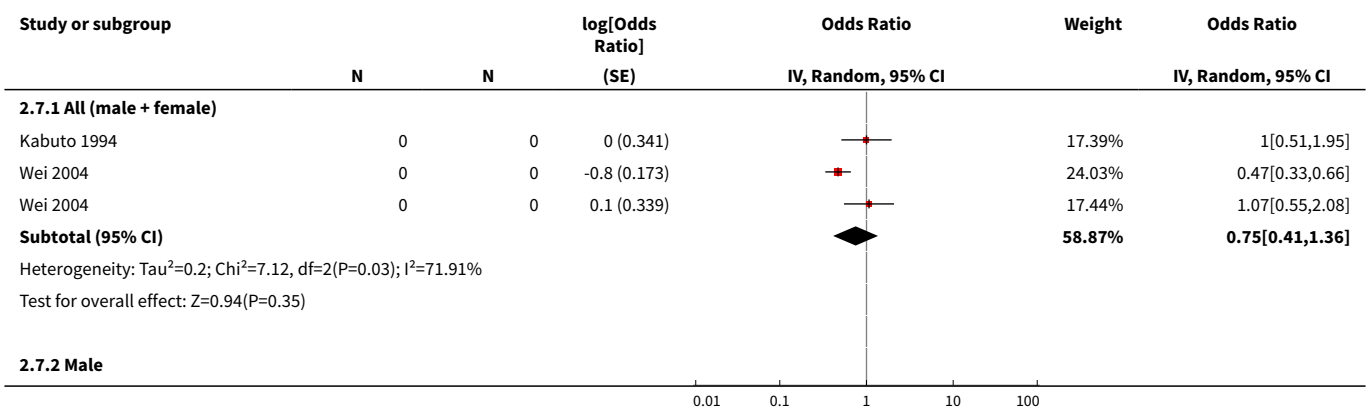


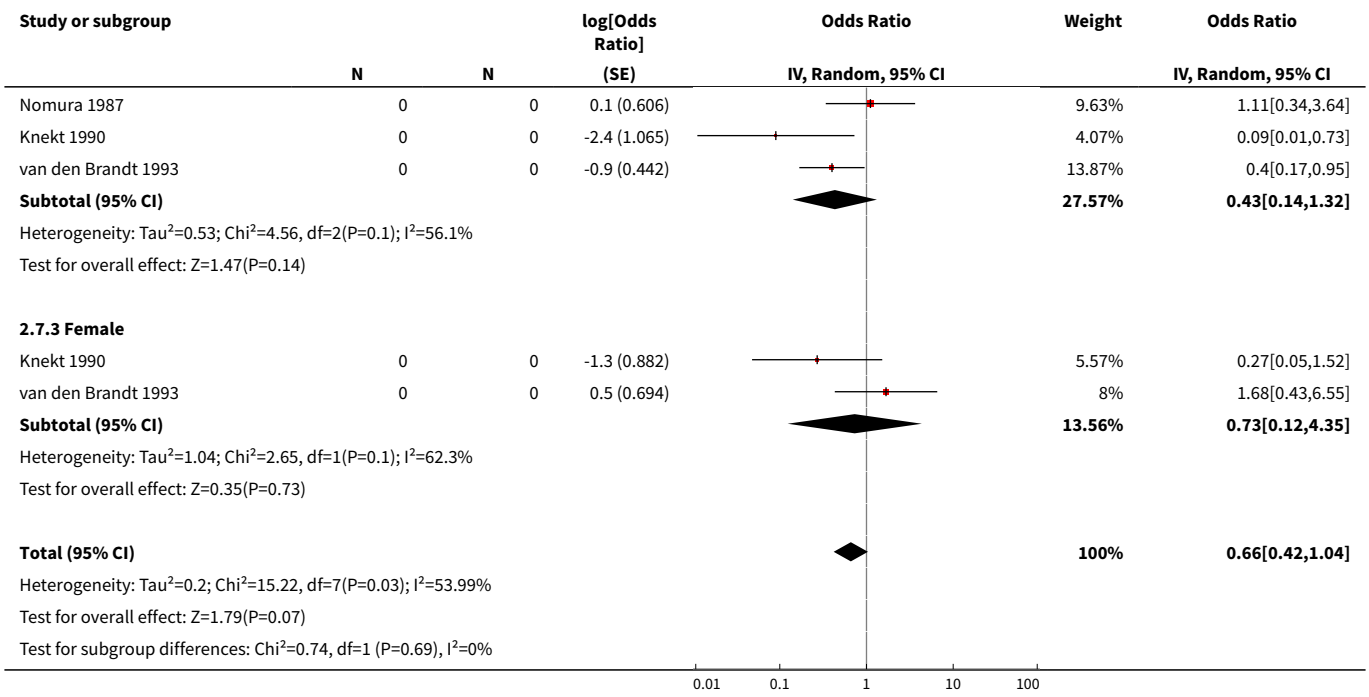


Analysis 2.6. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 6 Stomach cancer risk.

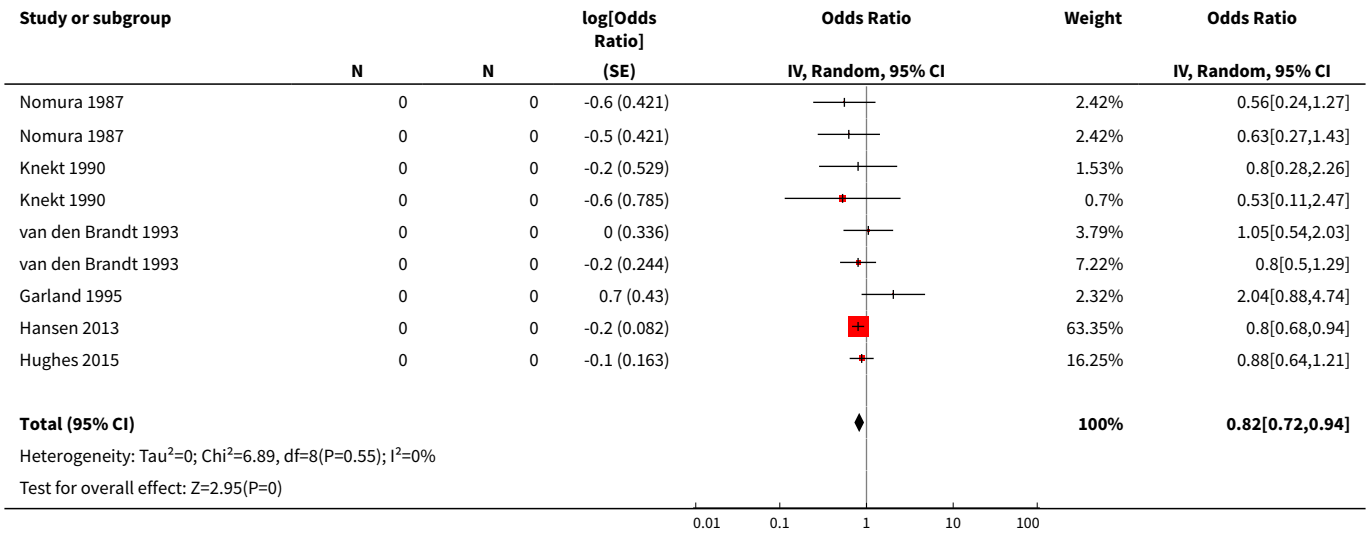


Analysis 2.7. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 7 Stomach cancer risk (by sex).



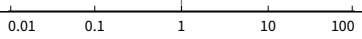


Analysis 2.8. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 8 Colorectal cancer risk.



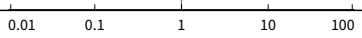
Analysis 2.9. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 9 Colorectal cancer risk (by sex).

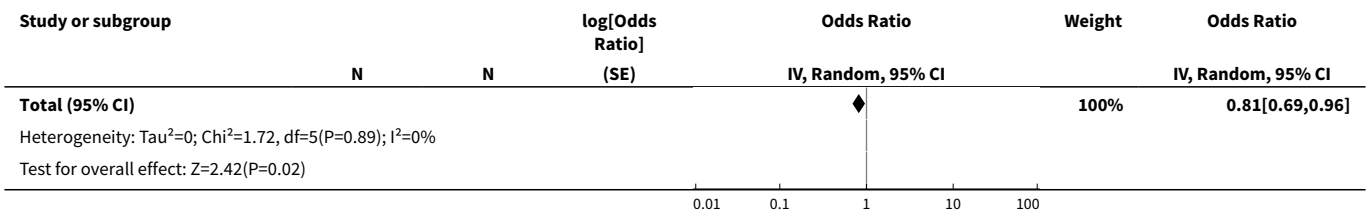
Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.9.1 All (male + female)						
Hansen 2013	0	0	-0.2 (0.082)		56.15%	0.8[0.68,0.94]
Subtotal (95% CI)					**56.15%**	**0.8[0.68,0.94]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.71(P=0.01)						
2.9.2 Male						
Nomura 1987	0	0	-0.5 (0.421)		2.91%	0.63[0.27,1.43]
Nomura 1987	0	0	-0.6 (0.421)		2.91%	0.56[0.24,1.27]
Knekt 1990	0	0	-0.6 (0.785)		0.85%	0.53[0.11,2.47]
van den Brandt 1993	0	0	-0.1 (0.402)		3.2%	0.91[0.41,2]
van den Brandt 1993	0	0	-0.2 (0.335)		4.58%	0.82[0.43,1.58]
Hughes 2015	0	0	0.2 (0.243)		8.52%	1.18[0.73,1.9]
Subtotal (95% CI)					**22.97%**	**0.86[0.65,1.16]**
Heterogeneity: Tau^2=0; Chi^2=3.76, df=5(P=0.58); I^2=0%						
Test for overall effect: Z=0.98(P=0.33)						
2.9.3 Female						
Knekt 1990	0	0	-0.2 (0.529)		1.86%	0.8[0.28,2.26]
van den Brandt 1993	0	0	-0.3 (0.323)		4.91%	0.77[0.41,1.45]
van den Brandt 1993	0	0	0.5 (0.501)		2.07%	1.58[0.59,4.22]
Garland 1995	0	0	0.7 (0.43)		2.8%	2.04[0.88,4.74]
Hughes 2015	0	0	-0.4 (0.233)		9.24%	0.64[0.41,1.01]
Subtotal (95% CI)					**20.88%**	**0.96[0.61,1.5]**
Heterogeneity: Tau^2=0.11; Chi^2=7.25, df=4(P=0.12); I^2=44.83%						
Test for overall effect: Z=0.18(P=0.85)						
Total (95% CI)					**100%**	**0.83[0.72,0.95]**
Heterogeneity: Tau^2=0; Chi^2=11.35, df=11(P=0.41); I^2=3.08%						
Test for overall effect: Z=2.6(P=0.01)						
Test for subgroup differences: Chi^2=0.68, df=1 (P=0.71), I^2=0%						



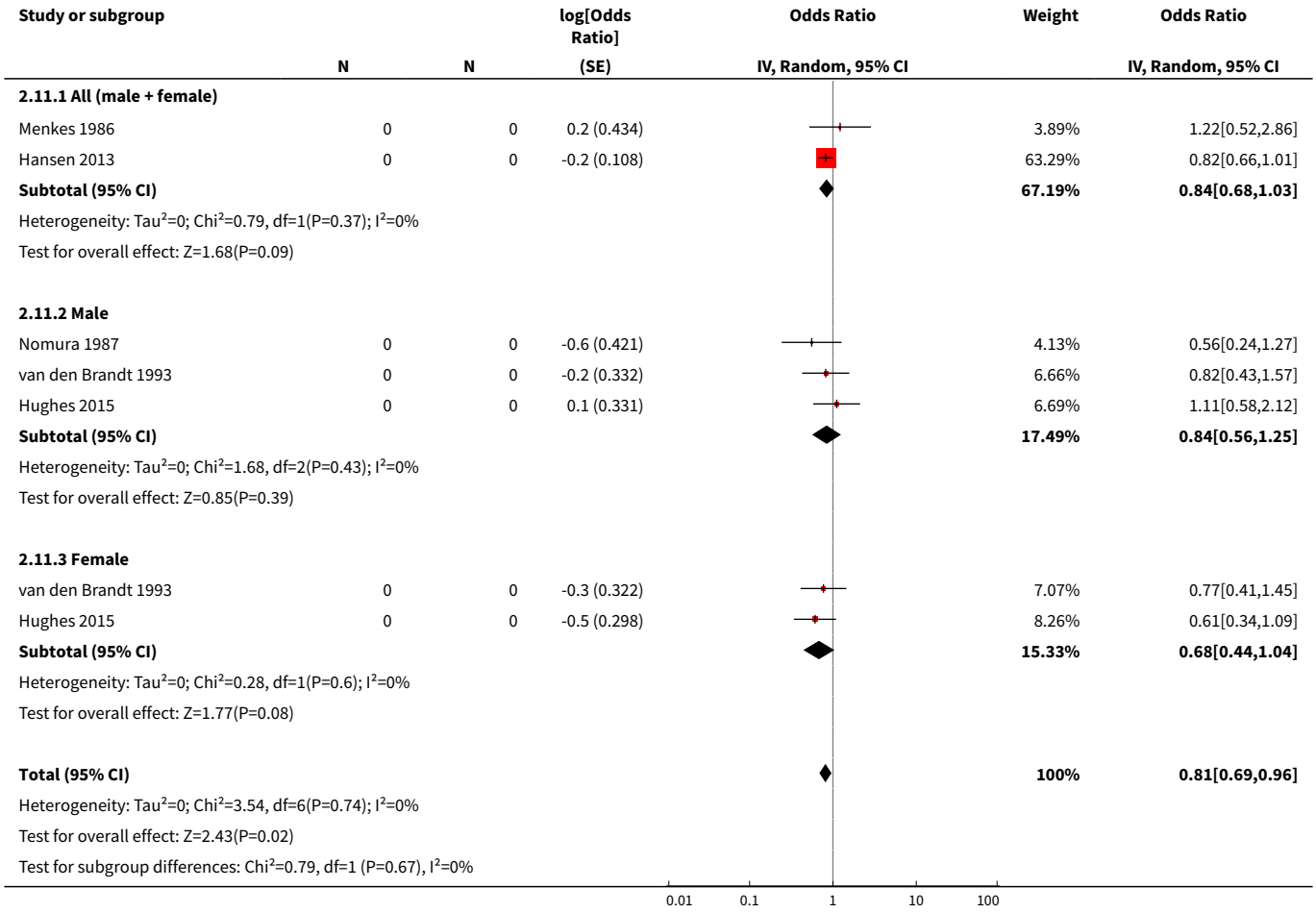
Analysis 2.10. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 10 Colon cancer risk.

Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Menkes 1986	0	0	0.2 (0.434)		3.85%	1.22[0.52,2.86]
Nomura 1987	0	0	-0.6 (0.421)		4.08%	0.56[0.24,1.27]
van den Brandt 1993	0	0	-0.2 (0.332)		6.58%	0.82[0.43,1.57]
van den Brandt 1993	0	0	-0.3 (0.322)		6.99%	0.77[0.41,1.45]
Hansen 2013	0	0	-0.2 (0.108)		62.53%	0.82[0.66,1.01]
Hughes 2015	0	0	-0.2 (0.213)		15.97%	0.81[0.53,1.23]

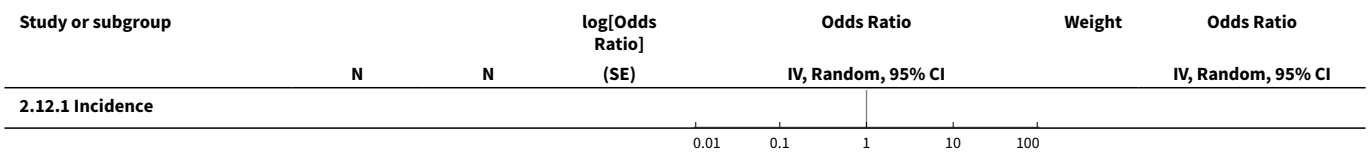


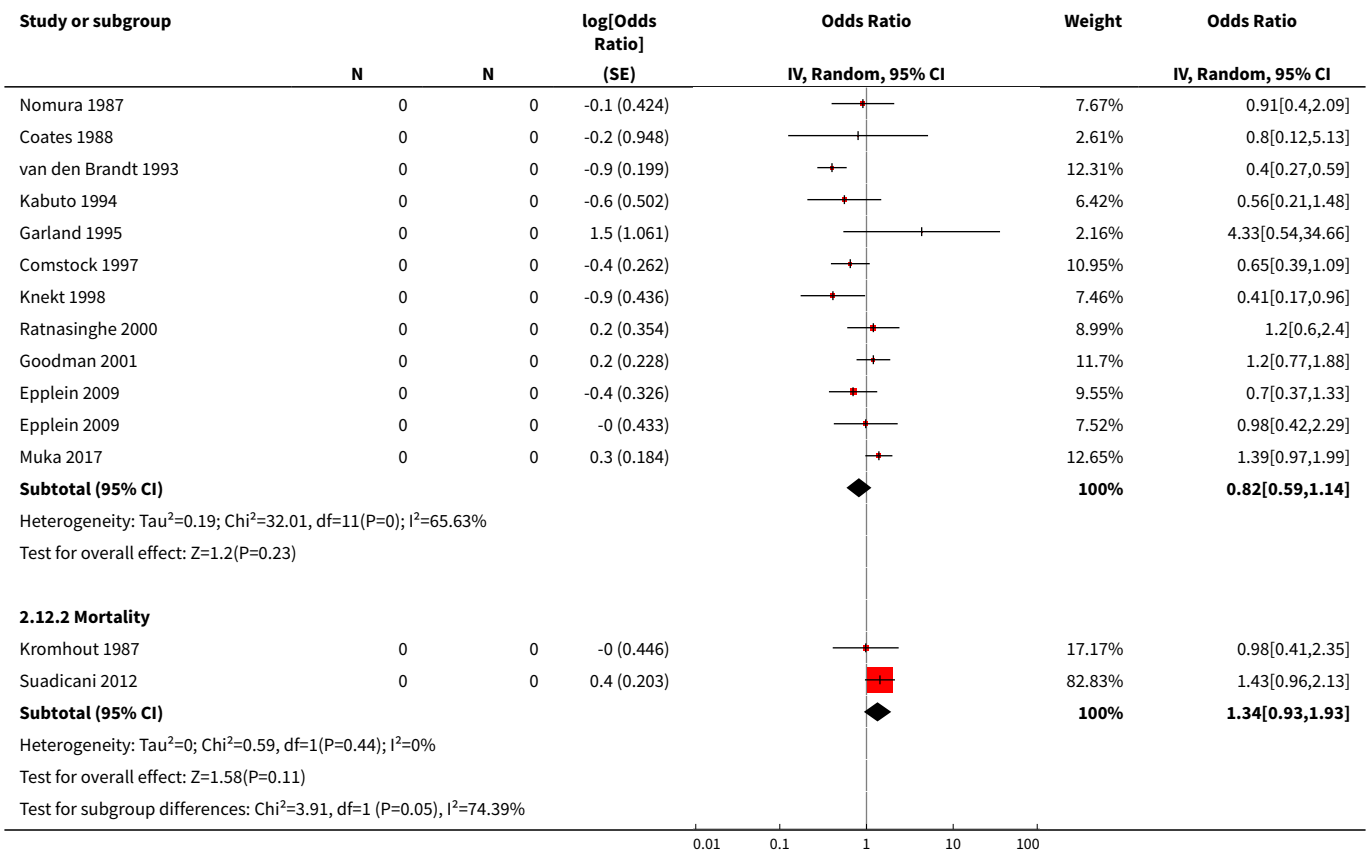


Analysis 2.11. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 11 Colon cancer risk (by sex).

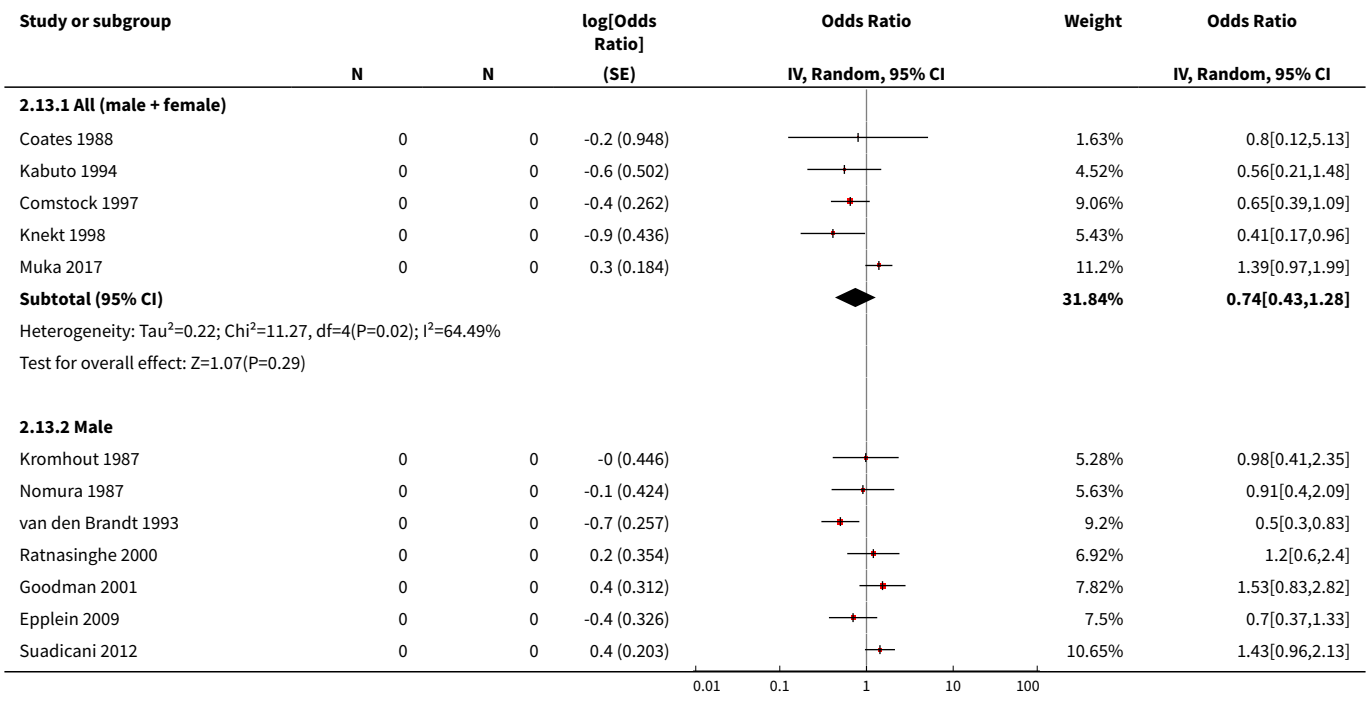


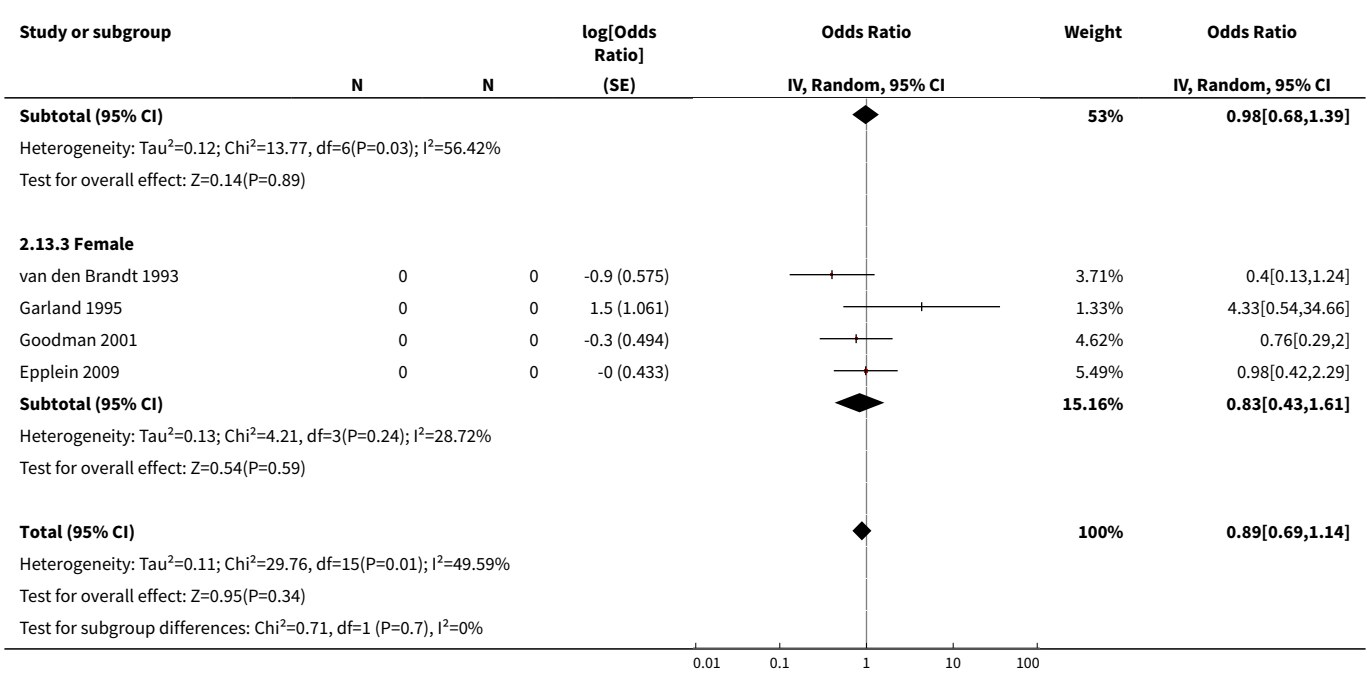
Analysis 2.12. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 12 Lung cancer incidence and mortality.



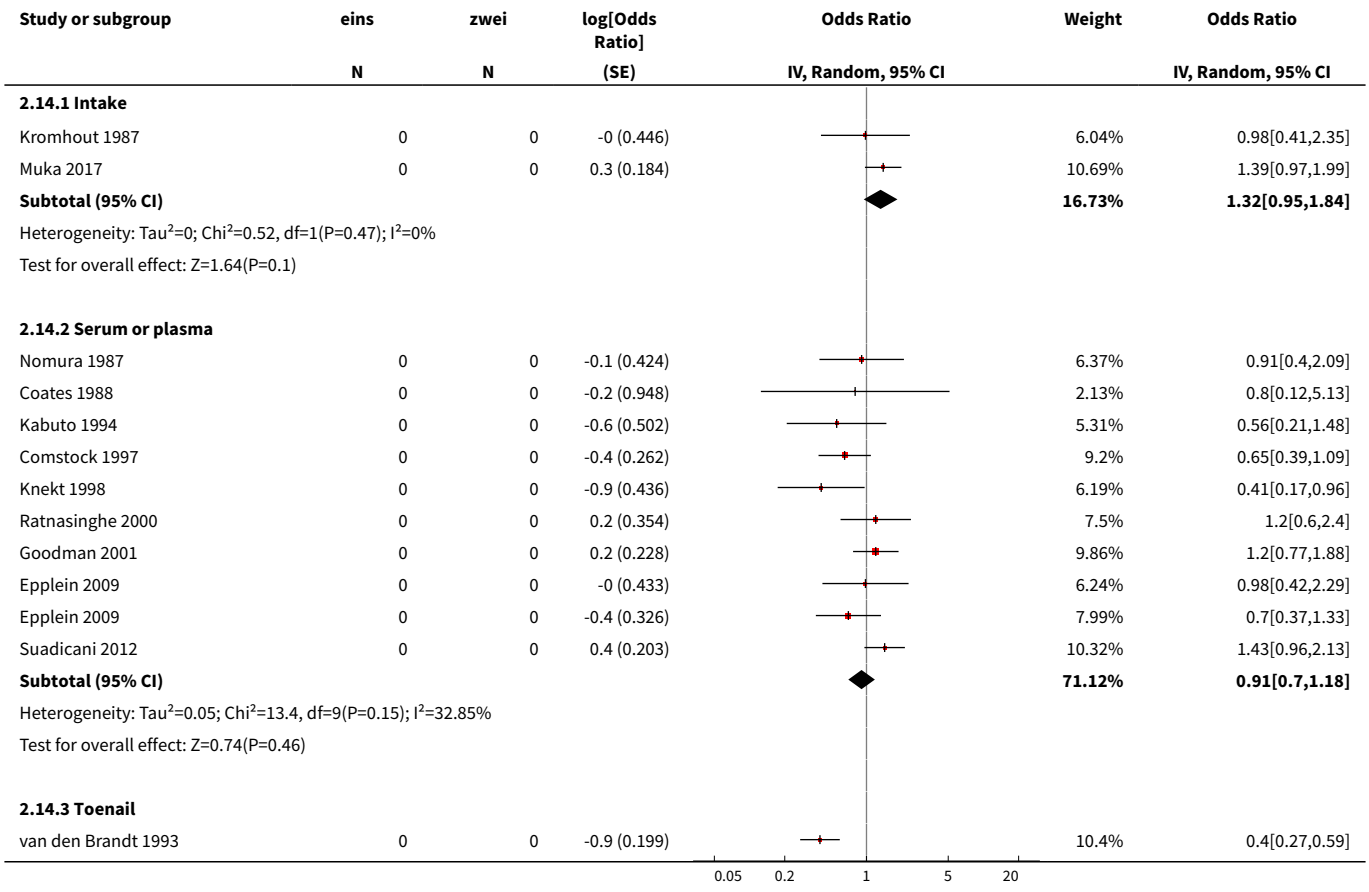


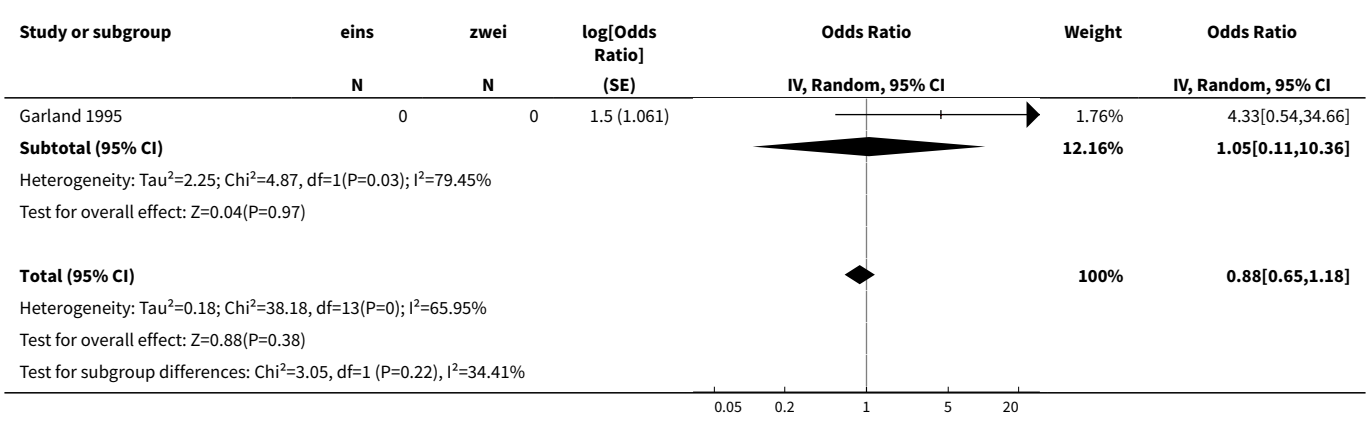
Analysis 2.13. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 13 Lung cancer risk (sex-disaggregated data).



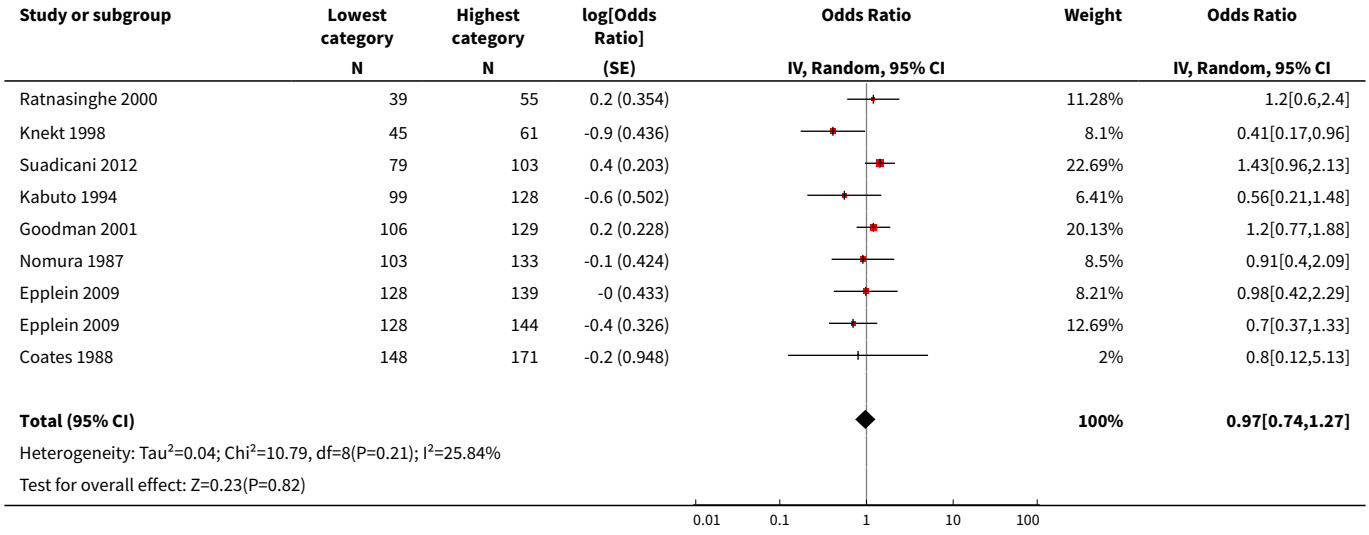


Analysis 2.14. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 14 Lung cancer risk (by exposure assessment).

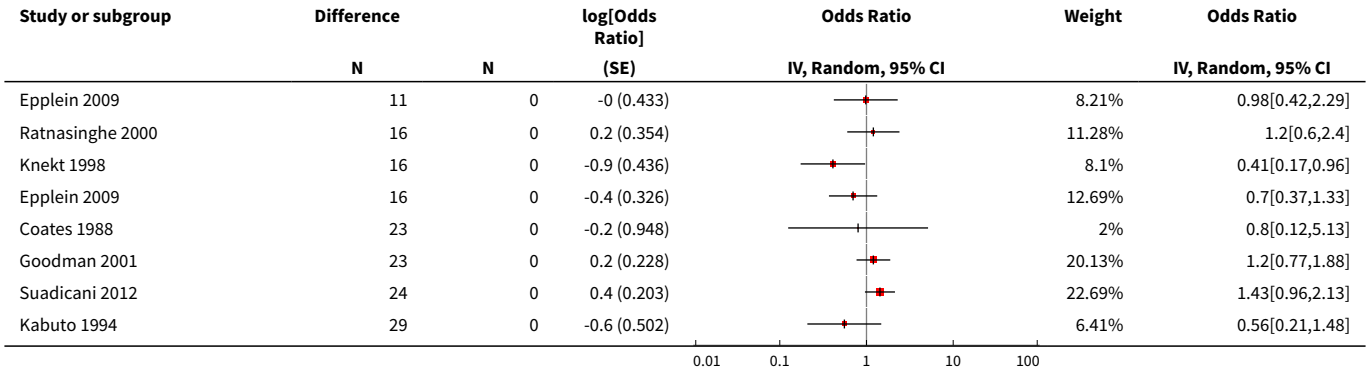




Analysis 2.15. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 15 Lung cancer risk (ascending order of selenium levels).



Analysis 2.16. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 16 Lung cancer risk (ascending order of differences in selenium levels).



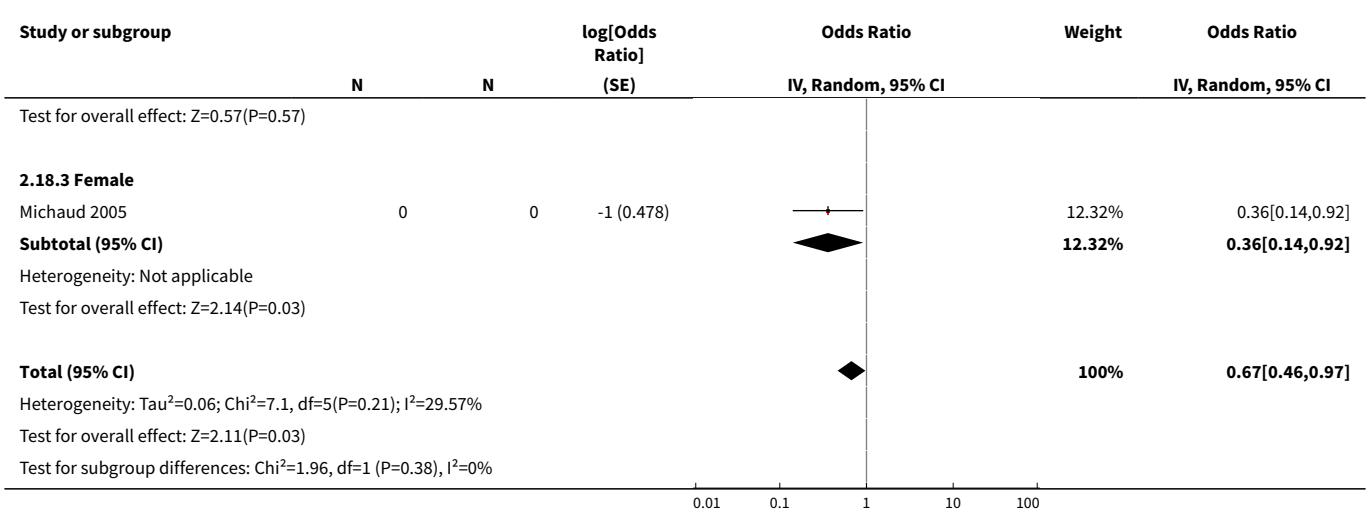
Study or subgroup	Difference N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Nomura 1987	30	0	-0.1 (0.424)		8.5%	0.91[0.4,2.09]
Total (95% CI)					**100%**	**0.97[0.74,1.27]**
Heterogeneity: Tau²=0.04; Chi²=10.79, df=8(P=0.21); I²=25.84%						
Test for overall effect: Z=0.23(P=0.82)						

Analysis 2.17. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 17 Breast cancer risk (women).

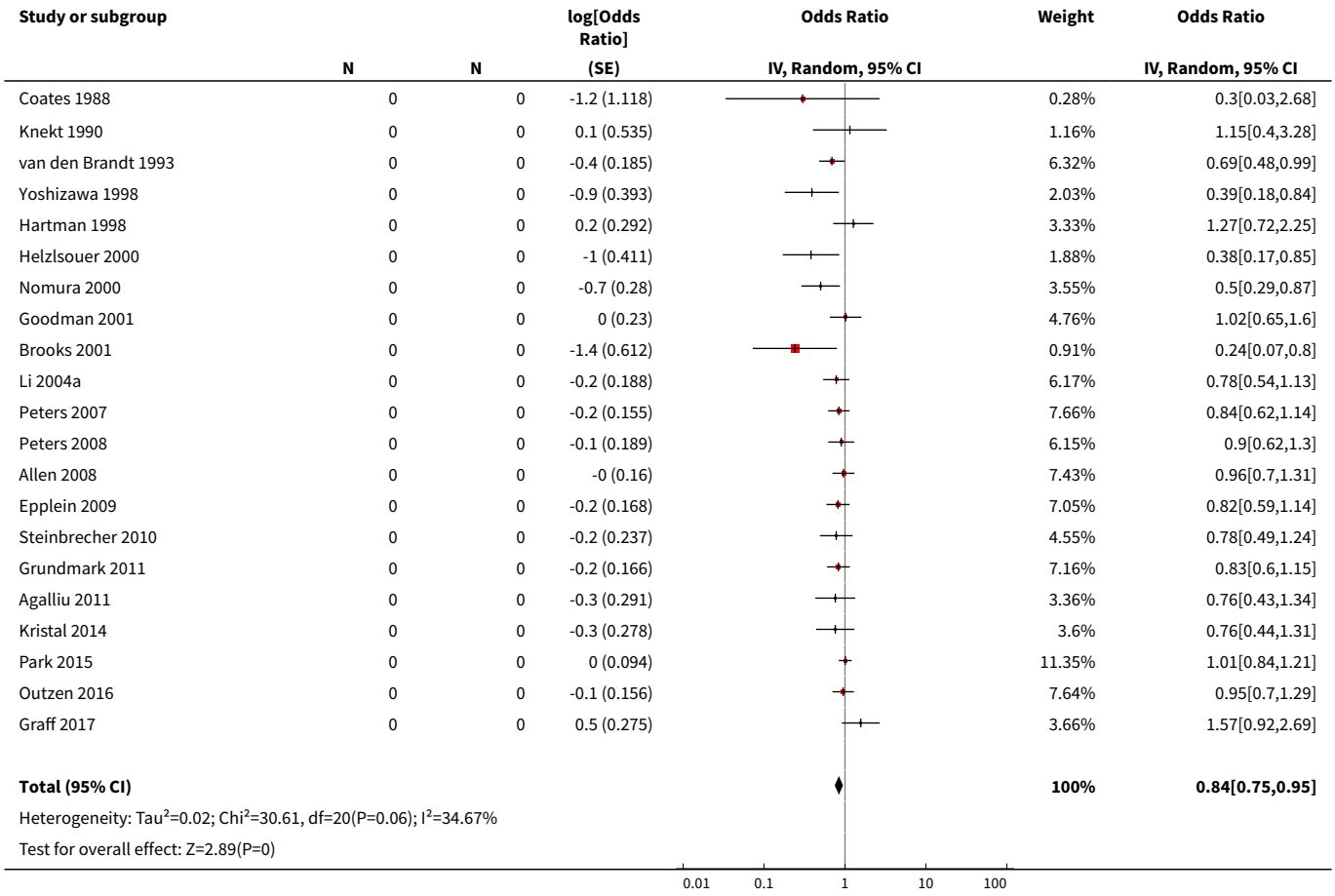
Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
van Noord 1987	0	0	0.1 (0.448)		6.28%	1.1[0.46,2.65]
Coates 1988	0	0	1.2 (0.597)		3.66%	3.4[1.06,10.95]
Knekt 1990	0	0	-0.4 (0.448)		6.29%	0.64[0.27,1.54]
Overvad 1991	0	0	0.2 (0.516)		4.83%	1.25[0.45,3.43]
van den Brandt 1993	0	0	-0.2 (0.213)		22.3%	0.84[0.55,1.28]
Garland 1995	0	0	0.1 (0.229)		20%	1.1[0.7,1.72]
Dorgan 1998	0	0	-0.1 (0.384)		8.37%	0.9[0.42,1.91]
Pantavos 2015	0	0	0.3 (0.181)		28.26%	1.34[0.94,1.91]
Total (95% CI)					**100%**	**1.09[0.87,1.37]**
Heterogeneity: Tau²=0.02; Chi²=8.15, df=7(P=0.32); I²=14.16%						
Test for overall effect: Z=0.75(P=0.45)						

Analysis 2.18. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 18 Bladder cancer risk.

Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.18.1 All (male + female)						
Menkes 1986	0	0	-0.7 (0.574)		9.12%	0.49[0.16,1.49]
van den Brandt 1993	0	0	-0.4 (0.19)		36.7%	0.67[0.46,0.97]
Subtotal (95% CI)					**45.82%**	**0.65[0.46,0.92]**
Heterogeneity: Tau²=0; Chi²=0.28, df=1(P=0.59); I²=0%						
Test for overall effect: Z=2.39(P=0.02)						
2.18.2 Male						
Nomura 1987	0	0	-1.1 (0.646)		7.44%	0.32[0.09,1.14]
Michaud 2002	0	0	-0.1 (0.543)		10.01%	0.87[0.3,2.52]
Michaud 2005	0	0	0.2 (0.292)		24.41%	1.17[0.66,2.07]
Subtotal (95% CI)					**41.86%**	**0.82[0.41,1.62]**
Heterogeneity: Tau²=0.15; Chi²=3.32, df=2(P=0.19); I²=39.78%						

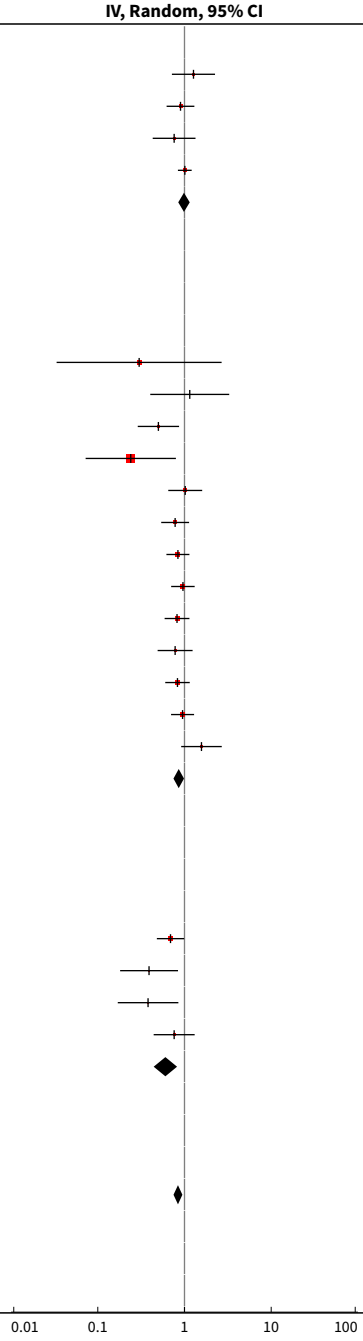


Analysis 2.19. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 19 Prostate cancer risk.



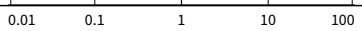
Analysis 2.20. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 20 Prostate cancer risk (by exposure assessment).

Study or subgroup	N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.20.1 Intake and supplement						
Hartman 1998	0	0	0.2 (0.292)		3.33%	1.27[0.72,2.25]
Peters 2008	0	0	-0.1 (0.189)		6.15%	0.9[0.62,1.3]
Agalliu 2011	0	0	-0.3 (0.291)		3.36%	0.76[0.43,1.34]
Park 2015	0	0	0 (0.094)		11.35%	1.01[0.84,1.21]
Subtotal (95% CI)					**24.18%**	**0.99[0.85,1.15]**
Heterogeneity: Tau^2=0; Chi^2=1.85, df=3(P=0.6); I^2=0%						
Test for overall effect: Z=0.18(P=0.86)						
2.20.2 Serum or plasma						
Coates 1988	0	0	-1.2 (1.118)		0.28%	0.3[0.03,2.68]
Knekt 1990	0	0	0.1 (0.535)		1.16%	1.15[0.4,3.28]
Nomura 2000	0	0	-0.7 (0.28)		3.55%	0.5[0.29,0.87]
Brooks 2001	0	0	-1.4 (0.612)		0.91%	0.24[0.07,0.8]
Goodman 2001	0	0	0 (0.23)		4.76%	1.02[0.65,1.6]
Li 2004a	0	0	-0.2 (0.188)		6.17%	0.78[0.54,1.13]
Peters 2007	0	0	-0.2 (0.155)		7.66%	0.84[0.62,1.14]
Allen 2008	0	0	-0 (0.16)		7.43%	0.96[0.7,1.31]
Epplein 2009	0	0	-0.2 (0.168)		7.05%	0.82[0.59,1.14]
Steinbrecher 2010	0	0	-0.2 (0.237)		4.55%	0.78[0.49,1.24]
Grundmark 2011	0	0	-0.2 (0.166)		7.16%	0.83[0.6,1.15]
Outzen 2016	0	0	-0.1 (0.156)		7.64%	0.95[0.7,1.29]
Graff 2017	0	0	0.5 (0.275)		3.66%	1.57[0.92,2.69]
Subtotal (95% CI)					**61.98%**	**0.86[0.75,0.99]**
Heterogeneity: Tau^2=0.02; Chi^2=16.1, df=12(P=0.19); I^2=25.46%						
Test for overall effect: Z=2.14(P=0.03)						
2.20.3 Toenail						
van den Brandt 1993	0	0	-0.4 (0.185)		6.32%	0.69[0.48,0.99]
Yoshizawa 1998	0	0	-0.9 (0.393)		2.03%	0.39[0.18,0.84]
Helzlsouer 2000	0	0	-1 (0.411)		1.88%	0.38[0.17,0.85]
Kristal 2014	0	0	-0.3 (0.278)		3.6%	0.76[0.44,1.31]
Subtotal (95% CI)					**13.83%**	**0.6[0.44,0.82]**
Heterogeneity: Tau^2=0.02; Chi^2=3.69, df=3(P=0.3); I^2=18.61%						
Test for overall effect: Z=3.2(P=0)						
Total (95% CI)					**100%**	**0.84[0.75,0.95]**
Heterogeneity: Tau^2=0.02; Chi^2=30.61, df=20(P=0.06); I^2=34.67%						
Test for overall effect: Z=2.89(P=0)						
Test for subgroup differences: Chi^2=8.01, df=1 (P=0.02), I^2=75.04%						



Analysis 2.21. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 21 Prostate cancer risk (ascending order of selenium levels).

Study or subgroup	Lowest category N	Highest category N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Knekt 1990	49	78	0.1 (0.535)		1.69%	1.15[0.4,3.28]
Allen 2008	62	84	-0 (0.16)		12.32%	0.96[0.7,1.31]
Grundmark 2011	70	81	-0.2 (0.166)		11.79%	0.83[0.6,1.15]
Outzen 2016	71	89	-0.1 (0.156)		12.72%	0.95[0.7,1.29]
Steinbrecher 2010	79	95	-0.2 (0.237)		7.07%	0.78[0.49,1.24]
Graff 2017	89	130	0.5 (0.275)		5.59%	1.57[0.92,2.69]
Li 2004a	92	124	-0.2 (0.188)		9.94%	0.78[0.54,1.13]
Goodman 2001	101	126	0 (0.23)		7.43%	1.02[0.65,1.6]
Brooks 2001	107	133	-1.4 (0.612)		1.31%	0.24[0.07,0.8]
Nomura 2000	119	147	-0.7 (0.28)		5.4%	0.5[0.29,0.87]
Peters 2007	127	158	-0.2 (0.155)		12.76%	0.84[0.62,1.14]
Epplein 2009	127	159	-0.2 (0.168)		11.58%	0.82[0.59,1.14]
Coates 1988	148	171	-1.2 (1.118)		0.4%	0.3[0.03,2.68]
Total (95% CI)					**100%**	**0.86[0.75,0.99]**
Heterogeneity: Tau²=0.02; Chi²=16.1, df=12(P=0.19); I²=25.46%						
Test for overall effect: Z=2.14(P=0.03)						



Analysis 2.22. Comparison 2 Observational studies: highest versus lowest selenium exposure, Outcome 22 Prostate cancer risk (ascending order of differences in selenium levels).

Study or subgroup	Difference N	N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Grundmark 2011	11	0	-0.2 (0.166)		11.79%	0.83[0.6,1.15]
Steinbrecher 2010	16	0	-0.2 (0.237)		7.07%	0.78[0.49,1.24]
Allen 2008	22	0	-0 (0.16)		12.32%	0.96[0.7,1.31]
Coates 1988	23	0	-1.2 (1.118)		0.4%	0.3[0.03,2.68]
Goodman 2001	25	0	0 (0.23)		7.43%	1.02[0.65,1.6]
Brooks 2001	26	0	-1.4 (0.612)		1.31%	0.24[0.07,0.8]
Nomura 2000	28	0	-0.7 (0.28)		5.4%	0.5[0.29,0.87]
Knekt 1990	29	0	0.1 (0.535)		1.69%	1.15[0.4,3.28]
Outzen 2016	29	0	-0.1 (0.156)		12.72%	0.95[0.7,1.29]
Peters 2007	31	0	-0.2 (0.155)		12.76%	0.84[0.62,1.14]
Epplein 2009	32	0	-0.2 (0.168)		11.58%	0.82[0.59,1.14]
Li 2004a	32	0	-0.2 (0.188)		9.94%	0.78[0.54,1.13]
Graff 2017	41	0	0.5 (0.275)		5.59%	1.57[0.92,2.69]
Total (95% CI)					**100%**	**0.86[0.75,0.99]**
Heterogeneity: Tau²=0.02; Chi²=16.1, df=12(P=0.19); I²=25.46%						
Test for overall effect: Z=2.14(P=0.03)						

ADDITIONAL TABLES

Table 1. Included observational studies by outcome

Organ system	Outcome	Number of studies/case definitions	Meta-analysis	Countries	Number of participants	Number of cases	Selenium assessment	Reporting study
Any cancer	Any cancer	total: 16 incidence: 7 mortality: 7 incidence and mortality combined: 1	✓ yes	USA Finland Netherlands Sweden Norway Belgium France China Japan	total: ~ 276,000	total: 6488 male: 3196 female: 1541	serum: 12 plasma: 2 serum + plasma: 1 dietary intake: 1	Willett 1983 Salonen 1984 Peleg 1985 Salonen 1985 Nomura 1987 Virtamo 1987 Coates 1988 Fex 1987 Kok 1987a Ringstad 1988 Knekt 1990 Kornitzer 2004 Akbaraly 2005 Bleys 2008 Fujishima 2011 Sun 2016
Gynaecological cancer	Female breast cancer	total: 8 incidence: 8 mortality: 0 incidence and mortality combined: 0	✓ yes	USA Finland Netherlands Channel Islands	total/female: 169,028	total/female: 1277	serum: 2 plasma: 1 serum + plasma: 1 toenail: 3 intake: 1	van Noord 1987 Coates 1988 Knekt 1990 Overvad 1991 van den Brandt 1993 Garland 1995 Dorgan 1998 Pantavos 2015
	Cervical cancer	total: 2 incidence: 2 mortality: 0	# no	USA	total/female: > 15,161	total/female: 62	serum: 2	Menkes 1986 Coates 1988

Table 1. Included observational studies by outcome *(Continued)*

		incidence and mortality combined: 0			(1 study did not report cohort size by sex)			
	Uterine cancer	total: 1 incidence: 1 mortality: 0 incidence and mortality combined: 0	# no	USA	total/female: 62,641	total/female: 91	toenail: 1	Garland 1995
	Ovarian cancer	total: 4 incidence: 4 mortality: 0 incidence and mortality combined: 0	# no	USA Finland	total/female: ~ 214,000	total/female: 568	serum: 2 toenail: 1 supplemental intake: 1	Menkes 1986 Knekt 1990 Garland 1995 Thomson 2008
	Gynaecological cancer (without breast cancer)	total: 1 incidence: 1 mortality: 0 incidence and mortality combined: 0	# no	Finland	total/female: 18,096	total/female: 86	serum: 1	Knekt 1990
Urological cancers	Renal cancer	total: 1 incidence: 1 mortality: 0 incidence and mortality combined: 0	# no	United Kindom	total: 23,658	total: 65	dietary intake: 1	Banim 2013
	Urinary bladder cancer	total: 6 incidence: 6 mortality: 0 incidence & mortality combined: 0	✓ yes	USA/ Hawaii Finland Netherlands	total: 279,100 female: 130,786 male: 128,009	total: 1295 female: 175 male 755	serum: 3 toenail: 3	Menkes 1986 Nomura 1987 van den Brandt 1993 Michaud 2002 Michaud 2005 Hotaling 2011
	Urinary tract cancer	total: 1 incidence: 1 mortality: 0	# no	Netherlands	total: 38,500	total: 47 male: 34 female: 13	serum: 1	Knekt 1990

Table 1. Included observational studies by outcome *(Continued)*

		incidence & mortality combined: 0						
Respiratory tract cancers	Lung cancer	total: 15 incidence: 13 mortality: 2 incidence and mortality combined: 0	✓ yes	China Japan USA Finland Netherlands Denmark	total: 371,067 male: 125,341 female: 181,895	total: 2223 male: 1384 female: 416	serum: 9 serum + plasma: 2 toenail: 2 dietary intake: 2 (1 study reported both serum levels and food intake)	Menkes 1986 Kromhout 1987 Nomura 1987 Coates 1988 Knekt 1990 van den Brandt 1993 Kabuto 1994 Garland 1995 Comstock 1997 Knekt 1998 Ratnasinghe 2000 Goodman 2001 Epplein 2009 Suadicani 2012 Muka 2017
	Oral/pharyngeal cancer	total: 1 incidence: 1 mortality: 0 incidence and mortality combined: 0	# no	USA	total: 20,305	total: 28	serum: 1	Menkes 1986
Andrological cancers	Prostate cancer	total: 21 incidence: 21 mortality: 0 incidence and mortality combined: 0	✓ yes	USA Canada Puerto Rico Europe	total/male: 576,667	total/male: 14,950	serum: 8 plasma: 5 toenail: 4 dietary intake: 4	Coates 1988 van den Brandt 1993 Hartman 1998 Yoshizawa 1998 Helzlsouer 2000 Nomura 2000 Brooks 2001 Goodman 2001 Li 2004a Peters 2007 Allen 2008

Table 1. Included observational studies by outcome *(Continued)*

								Peters 2008 Epplein 2009 Kristal 2014 Park 2015 Outzen 2016 Graff 2017
Gastrointestinal cancers	Oesophageal cancer	total: 2 incidence: 2 mortality: 1 incidence and mortality combined: 0	# no	China USA	total: 29,923	total: > 959	serum: 1 supplemental intake: 1	Wei 2004 Dong 2008
	Oesophageal squamous cell carcinoma	total:*2* incidence: 2 mortality: 0 incidence and mortality combined: 0	# no	Netherlands Iran	total: 168,257	total: 265	toenail: 1 intake: 1	Steinbrecher 2010 Hashemian 2015
	Oesophageal adenocarcinoma	total:*1* incidence:*1* mortality:*0* incidence and mortality combined: 0	# no	Netherlands	total: 120,852	total: 112	toenail: 1	Steinbrecher 2010
	Oesophageal/stomach cancer	total: 1 incidence: 1 mortality: 0 incidence and mortality combined: 0	# no	Netherlands	total: 36,265	total: 86 male: 51 female: 35	serum: 1	Knekt 1998
	Gastric cardia adenocarcinoma	total:*1* incidence:*1* mortality:*0* incidence and mortality combined: 0	# no	Netherlands	total: 120,852	total:114	toenail: 1	Steinbrecher 2010

Table 1. Included observational studies by outcome *(Continued)*

Stomach cancer	total: 5 incidence: 5 mortality: 1 incidence and mortality combined: 0	✓ yes	China Japan USA/ Hawaii Finland Nether-lands	total: ~ 197,000 male: 86,311 female: 80,669	total: 955 male: 626 female: 329	serum: 4 toenail: 1	Nomura 1987 Knekt 1990 van den Brandt 1993 Kabuto 1994 Wei 2004
Primary liver can-cer	total: 4 incidence: 3 mortality: 1 incidence and mortality combined: 0	# no	China Europe Taiwan	total: 701,809 male: 61,470 female: 74,941	total: 877 male: 567 female: 204	plasma: 1 serum: 1 toenail: 1 intake: 1	Yu 1999 Sakoda 2005 Hughes 2016 Ma 2017
Pancreatic cancer	total: 4 incidence: 4 mortality: 0 incidence and mortality combined: 0	# no	USA Finland UK	total: 159,062	total: 311 male: 69 female: 84	serum: 2 intake: 1 supplemental in-take: 1	Menkes 1986 Knekt 1990 Banim 2013 Han 2013
Colorectal cancer	total: 6 incidence: 6 mortality: 0 incidence and mortality combined: 0	✓ yes	USA/ Hawaii Europe	total: 712,746 male: 216,272 female: 442,266	total: 2627 male: 810 female: 797	serum: 3 toenail: 2 supplement use: 1	Nomura 1987 Knekt 1990 van den Brandt 1993 Garland 1995 Hansen 2013 Hughes 2015
Colon can-cer	total: 5 incidence: 5 mortality: 0 incidence and mortality combined: 0	✓ yes	USA/ Hawaii Europe	total: 636,641 male: 195,100 female: 361,529	total: 1677 male: 525 female: 510	serum: 3 toenail: 1 supplement use: 1	Menkes 1986 Nomura 1987 van den Brandt 1993 Hansen 2013 Hughes 2015
Rectal cancer	total: 4	# no	USA/ Hawaii	total: 610,837	total: 861	serum: 2	Nomura 1987

Table 1. Included observational studies by outcome *(Continued)*

		incidence: 4 mortality: 0 incidence and mortality combined: 0		Europe	male: 195,100 female: 361,529	male: 303 female: 210	toenail: 1 supplement use:1	van den Brandt 1993 Hansen 2013 Hughes 2015
	All gastrointestinal cancers	total: 1 incidence: 1 mortality: 0 incidence and mortality combined: 0	# no	USA	total: 6,167	total: 143	plasma and serum: 1	Coates 1988
Skin cancer	Melanoma	total: 3 incidence: 3 mortality: 0 incidence and mortality combined: 0	# no	USA	total: ~ 158,000	total: 547	serum: 1 toenail: 1 supplemental intake: 1	Menkes 1986 Garland 1995 Peters 2008
	Basal cell carcinoma	total: 3 incidence: 3 mortality: 0 incidence and mortality combined: 0	# no	Australia USA Finland	total: > 66,000	total: 292	serum: 3 dietary intake: 1	Menkes 1986 Knekt 1990 McNaughton 2005
	Squamous cell carcinoma	total: 4 incidence: 4 mortality: 0 incidence and mortality combined: 0	# no	Australia USA	total: ~ 30,000	total: 488	serum: 2 plasma: 1 dietary intake: 1	Menkes 1986 Combs 1993 Karagas 1997 McNaughton 2005
	Total non-melanoma skin cancer	total: 1 incidence: 1 mortality: 0 incidence and mortality combined: 0	# no	USA	total: 117	total: 19	plasma: 1	Clark 1985
Rare and other cancers	Haematological cancers	total: 1 incidence: 1 mortality: 0	# no	USA	total: 6167	total: 12	serum + plasma: 1	Coates 1988

Table 1. Included observational studies by outcome *(Continued)*

	incidence and mortality combined: 0						
Thyroid cancer	total: 2 incidence: 2 mortality: 0 incidence and mortality combined: 0	# no	Norway	total: 582,807 male: 287,944 female: 194,863	total: 635 male: 269 female: 366	serum: 1 intake:1	Glattre 1989 O'Grady 2014
Other cancers	total: 4 incidence: 3 mortality: 1 incidence and mortality combined: 0	# no	China USA Finland	total: 109,179 male: 21,172 female: 80,737	total: 512 male: 169 female: 285	serum: 2 serum + plasma: 1 toenail: 1	Coates 1988 Knekt 1990 Garland 1995 Wei 2004

Some studies did not report the sex of participants or cancer cases; consequently, figures for women and men do not always sum up to the total number of participants or cancer cases.

Table 2. Risk of bias: observational studies *(Continued)*

Study	Publication	Newcastle-Ottawa Scale (cohort)				Newcastle-Ottawa Scale (case-control)			
		Selection	Comparability	Outcome	Total	Selection	Comparability	Exposure	Total
Agalliu 2011	Agalliu 2011	0-1-0-1	1	1-1-0	5	0-1-0-1	1	1-1-0	5
Akbaraly 2005	Akbaraly 2005	0-1-1-1	2	0-1-0	6	.-.-.-.	.	.-.-.	.
Allen 2008	Allen 2008	1-1-1-1	2	1-1-0	8	1-1-1-1	2	1-1-1	9
Banim 2013	Banim 2013	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9

Table 2. Risk of bias: observational studies *(Continued)*

	Barrass 2013	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9
Bleys 2008	Bleys 2008	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
	Goyal 2013	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Brooks 2001	Brooks 2001	0-1-1-0	2	1-0-0	5	1-0-1-1	2	1-1-0	7
Clark 1985	Clark 1985	0-1-1-0	0	0-0-0	2	.-.-.-.	.	.-.-.	.
Coates 1988	Coates 1988	0-1-1-0	1	1-1-0	5	1-0-1-0	1	1-1-1	6
	Coates 1987	.-.-.-.	.	.-.-.	.	.-.-.-.	.	.-.-.	.
Combs 1993	Combs 1993	0-1-1-0	2	1-0-0	5	.-.-.-.	.	.-.-.	.
Comstock 1997	Comstock 1997	0-1-1-0	2	1-1-0	6	1-1-1-1	2	1-1-1	9
Dong 2008	Dong 2008	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Dorgan 1998	Dorgan 1998	0-1-1-1	2	0-1-0	6	1-1-1-1	2	1-1-1	9
Epplein 2009	Epplein 2009	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
	Gill 2009	0-1-1-1	1	1-1-0	6	0-1-1-1	1	1-1-1	7

Table 2. Risk of bias: observational studies *(Continued)*

Fex 1987	Fex 1987	1-1-1-0	2	1-1-1	8	1-0-1-1	2	1-1-1	8
Fujishima 2011	Fujishima 2011	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Garland 1995	Garland 1995	0-1-1-1	2	1-1-1	8	1-1-1-1	2	1-1-1	9
	Hunter 1990	0-1-1-1	2	1-1-1	8	1-1-1-1	2	1-1-1	9
Glattre 1989	Glattre 1989	0-1-1-0	1	1-1-1	6	1-1-1-1	1	1-1-1	8
Goodman 2001	Goodman 2001	0-1-1-0	2	1-1-0	6	1-1-1-1	2	1-1-1	9
Graff 2017	Graff 2017	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
Grundmark 2011	Grundmark 2011	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Han 2013	Han 2013	0-1-0-1	2	1-1-0	7	.-.-.-.	.	.-.-.	.
Hansen 2013	Hansen 2013	0-1-1-1	1	1-1-1	7	.-.-.-.	.	.-.-.	.
Hartman 1998	Hartman 1998	1-1-0-1	2	1-1-0	7	.-.-.-.	.	.-.-.	.
Hashemian 2015	Hashemian 2015	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.

Table 2. Risk of bias: observational studies *(Continued)*

Helzlsouer 2000	Helzlsouer 2000	0-1-1-1	1	1-1-0	6	1-1-1-1	1	1-1-1	8
Hughes 2015	Hughes 2015	1-1-1-1	2	0-1-0	7	0-1-1-1	2	1-1-1	8
Hughes 2016	Hughes 2016	1-1-1-1	2	0-1-1	8	0-1-1-1	2	1-1-1	8
Kabuto 1994	Kabuto 1994	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
Karagas 1997	Karagas 1997	0-1-1-1	2	1-1-1	8	1-1-1-1	2	1-1-1	9
Knekt 1990	Knekt 1990	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
	Hakama 1990	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
	Knekt 1988	1-1-1-1	2	1-1-1	9	0-0-1-1	2	1-1-1	7
	Knekt 1996	1-1-1-1	1	1-1-1	8	0-1-1-1	1	1-1-1	7
	Knekt 1991	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
Knekt 1998	Knekt 1998	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
Kok 1987a	Kok 1987b	1-1-1-1	2	1-1-1	9	1-0-1-1	2	1-1-1	8

Table 2. Risk of bias: observational studies *(Continued)*

	Kok 1987a	.-.-.-.	.	.-.-.	.	.-.-.-.	.	.-.-.	.
Kornitzer 2004	Kornitzer 2004	1-1-1-0	1	1-1-1	7	1-1-1-1	1	1-1-1	8
Kristal 2014	Kristal 2014	1-1-1-1	1	1-1-1	8	1-1-1-1	1	1-1-1	8
Kromhout 1987	Kromhout 1987	1-1-1-0	2	1-1-1	8	.-.-.-.	.	.-.-.	.
Li 2004a	Li 2004a	0-1-1-1	2	0-1-1	7	1-1-1-1	2	1-1-1	9
Ma 2017	Ma 2017	1-1-1-1	2	1-1-0	8	.-.-.-.	.	.-.-.	.
McNaughton 2005	McNaughton 2005	1-1-1-1	1	1-1-0	7	1-1-1-1	1	1-1-1	8
	Heinen 2007	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
	van der Pols 2009	1-1-1-1	2	1-1-0	8	.-.-.-.	.	.-.-.	.
Menkes 1986	Menkes 1986	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
	Batieha 1993	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
	Breslow 1995	0-1-1-1	2	1-1-0	7	1-0-1-1	2	1-1-1	8

Table 2. Risk of bias: observational studies *(Continued)*

	Burney 1989	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
	Helzlsouer 1996	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
	Helzlsouer 1989	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
	Ko 1994	0-1-1-0	2	1-1-0	6	1-1-1-1	2	1-1-1	9
	Menkes 1986	-.-.-.	.	.-.-.	.	.-.-.-.	.	.-.-.	.
	Schober 1987	0-1-1-1	1	1-1-0	6	0-1-1-1	1	1-1-1	7
	Schober 1986	.-.-.	.	.-.-.	.	.-.-.-.	.	.-.-.	.
	Zheng 1993	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
Michaud 2002	Michaud 2002	1-1-1-1	2	1-1-0	8	0-1-1-1	2	1-1-1	8
Michaud 2005	Michaud 2005	0-1-1-1	2	0-1-0	6	1-1-1-1	2	1-1-1	9
Muka 2017	Muka 2017	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Nomura 1987	Nomura 1987	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9

Table 2. Risk of bias: observational studies *(Continued)*

Nomura 2000	Nomura 2000	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9
O'Grady 2014	O'Grady 2014	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Outzen 2016	Outzen 2016	1-1-1-1	2	1-1-1	9	1-0-1-1	2	1-1-1	8
Overvad 1991	Overvad 1991	1-1-1-0	1	1-1-0	6	.-.-.-.	.	.-.-.	.
Pantavos 2015	Pantavos 2015	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Park 2015	Park 2015	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
Peleg 1985	Peleg 1985	1-1-1-1	1	1-1-0	7	1-1-1-1	1	1-1-1	8
Peters 2007	Peters 2007	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
Peters 2008	Peters 2008	0-1-1-1	1	1-1-1	7	.-.-.-.	.	.-.-.	.
	Asgari 2009	0-1-1-1	1	1-1-0	6	.-.-.-.	.	.-.-.	.
	Hotaling 2011	0-1-0-1	0	1-1-1	5	.-.-.-.	.	.-.-.	.

Table 2. Risk of bias: observational studies *(Continued)*

	Walter 2011	0-1-0-1	2	1-1-1	7	.-.-.-.	.	.-.-.	.
Ratnasinghe 2000	Ratnasinghe 2000	1-1-1-1	2	1-0-0	7	0-0-1-1	2	1-1-1	7
Ringstad 1988	Ringstad 1988	1-1-1-1	2	1-1-0	8	1-1-1-1	2	1-1-1	9
Thomson 2008	Thomson 2008	0-1-1-1	2	0-1-0	6	.-.-.-.	.	.-.-.	.
Sakoda 2005	Sakoda 2005	0-1-1-0	1	1-1-0	5	1-1-1-1	1	1-1-1	8
Salonen 1984	Salonen 1984	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
Salonen 1985	Salonen 1985	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9
Steinbrecher 2010	Steinbrecher 2010	1-1-1-1	2	0-1-0	7	1-1-1-1	2	0-1-1	8
Suadicani 2012	Suadicani 2012	0-1-1-1	2	1-1-1	8	.-.-.-.	.	.-.-.	.
Sun 2016	Sun 2016	1-1-1-1	2	1-1-0	8	.-.-.-.	.	.-.-.	.
van den Brandt 1993	van den	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.

Table 2. Risk of bias: observational studies *(Continued)*

	Brandt 1993								
	van den Brandt 1994	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
	van den Brandt 1993	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
	van den Brandt 2003	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
	Zeegers 2002	1-1-1-1	2	1-1-1	9	.-.-.-.	.	.-.-.	.
	Steevens 2010	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-0	6
van Noord 1987	van Noord 1987	1-1-1-0	1	1-0-1	6	1-1-1-0	1	1-1-1	7
Virtamo 1987	Virtamo 1987	0-1-1-1	2	1-1-1	8	.-.-.-.	.	.-.-.	.
Wei 2004	Wei 2004	1-1-1-1	1	1-1-1	8	.-.-.-.	.	.-.-.	.
	Mark 2000	1-1-1-1	1	1-1-1	8	.-.-.-.	.	.-.-.	.
Willett 1983	Willett 1983	1-1-1-0	2	1-1-0	7	1-1-1-1	2	1-1-1	9

Table 2. Risk of bias: observational studies *(Continued)*

Yoshizawa 1998	Yoshizawa 1998	0-1-1-1	2	1-1-1	8	1-0-1-1	2	1-1-1	8
Yu 1999	Yu 1999	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9

Table 3. Results of observational studies not included in meta-analysis

Organ system	Cancer	Case definition	Risk ratio estimate (highest vs lowest exposure category)	95% CI	Selenium marker	Sex	Study
Gynaecological	Cervix	incidence	0.89	0.40 to 2.00	serum	women	Menkes 1986 (Batieha 1993)
			1.10	n.r.	serum		Coates 1988
	Gynaecological (without breast)	incidence	0.96	n.r.	serum		Knekt 1990
	Ovary	incidence	0.87	0.25 to 5.26	serum		Knekt 1990 (Knekt 1996)
			1.22	0.44 to 3.38	toenail		Garland 1995
			0.58	0.2 to 1.7	serum		Menkes 1986 (Helzlsour 1996)
			1.00	0.73 to 1.37	suppl. intake		Thomson 2008
	Uterus	incidence	1.38	0.62 to 3.08	toenail		Garland 1995
Gastrointestinal	Gastrointestinal tract (all)	incidence	1.00	n.r.	serum/plasma	both	Coates 1988
	Oesophageal squamous cell carcinoma	incidence	0.37	0.16 to 0.86	toenail	both	Steevens 2010
			0.67	0.53 to 1.30	intake	both	Hashemian 2015

Table 3. Results of observational studies not included in meta-analysis *(Continued)*

Oesophageal adenocarcinoma	incidence	0.76	0.41 to 1.40	toenail	both	Steevens 2010
Oesophagus	incidence	0.56	0.44 to 0.71	serum	both	Wei 2004 (Mark 2000)
	mortality	0.62	0.44 to 0.89	serum		
	mortality	0.35	0.16 to 0.81	serum	both	Wei 2004 (Wei 2004)
	incidence	0.27	0.03 to 2.21	suppl. intake	both	Dong 2008
Gastric cardio adenocarcinoma	incidence	0.52	0.27 to 1.02	toenail	both	Steevens 2010
Oesophagus and stomach	incidence	0.45	n.r.	serum	men	Knekt 1990 (Knekt 1988)
	incidence	0.67	n.r.	serum	women	
Liver	incidence	0.62	0.21 to 1.86	plasma	men	Yu 1999
		0.41	0.23 to 0.72	serum	both	Hughes 2016
		0.86	0.52 to to 1.43	intake	both	Ma 2017
		0.95	0.51 to 1.76		men	
		0.70	0.26 to 1.90		women	
	mortality	0.50	0.28 to 0.90	toenail	both	Sakoda 2005
		0.57	0.31 to 1.05		men	
		0.18	0.03 to 1.13		women	
Pancreas	incidence	0.08	0.01 to 0.56	serum	men	Menkes 1986 (Burney 1989)
		0.83	0.40 to 1.67		women	
		0.58	n.r.	serum	men	Knekt 1990
		3.49	n.r.		women	

Table 3. Results of observational studies not included in meta-analysis *(Continued)*

			0.72	0.36 to 1.43	intake	both	Banim 2013
			0.69	0.39 to 1.20	supplemental intake	both	Han 2013
	Rectum	incidence	0.625	n.r.	serum	men	Nomura 1987
			1.05	0.54 to 2.03	toenail	both	van den Brandt 1993
			0.91	0.41 to 2.00		men	
			1.58	0.59 to 4.22		women	
			0.80	0.68 to 0.95	supplement use	both	Hansen 2013
			1.09	0.63 to 1.89	serum	both	Hughes 2015
			1.32	0.55 to 3.19		men	
			0.76	0.32 to 1.80		women	
Urological cancers	Renal cancer	incidence	0.40	0.17 to 0.98	dietary intake	both	Banim 2013
	Urinary tract (all)	incidence	0.97	0.72 to 1.31	serum	both	Hotaling 2011
			0.81	n.r.	serum	men	Knekt 1990
			4.12	n.r.		women	
Respiratory tract	Cavum oris/pharynx	incidence	5.43	n.r.	serum	both	Menkes 1986 (Zheng 1993)
Skin	Melanoma	incidence	1.66	0.71 to 3.85	toenail	women	Garland 1995
			0.90	0.30 to 2.50	serum	both	Menkes 1986 (Breslow 1995)
			0.98	0.69 to 1.41	suppl. intake	both	Peters 2008 (Asgari 2009)
	Any non-melanoma cancer	incidence	0.77	n.r.	plasma	both	Clark 1985

Table 3. Results of observational studies not included in meta-analysis *(Continued)*

	Basal cell carcinoma	incidence	0.54	n.r.	serum	men	Knekt 1990
			1.55	n.r.		women	
			0.80	0.10 to 4.5	serum	both	Menkes 1986 (Breslow 1995)
			0.86	0.38 to 1.96	serum	both	McNaughton 2005
			0.95	0.59 to 1.50	intake		
	Squamous cell carcinoma	incidence	0.69	0.51 to 0.92	plasma	both	Combs 1993
			0.60	0.20 to 1.50	serum	both	Menkes 1986 (Breslow 1995)
			0.86	0.47 to 1.58	plasma	both	Karagas 1997
			1.30	0.77 to 2.3	intake	both	McNaughton 2005
			0.49	0.24 to 0.99	serum		
Other	Haematological	incidence	0.60	n.r.	serum/plasma	both	Coates 1988
		incidence	0.95	0.75 to 1.20	suppl. intake	both	Walter 2011
	Thyroid	incidence	0.13	0.02 to 0.77	serum	both	Glattre 1989
			0.15	0.0 to 5.0		men	
			0.12	0.01 to 1.11		women	
			1.35	0.99 to 1.84	intake	both	O'Grady 2014
			1.23	0.71 to 2.12		men	
			1.14	1.65 to 2.02		women	

n.r. = not reported.

APPENDICES

Appendix 1. Electronic search strategies

Database	Date of most recent literature search	Search strategy	Comment
www.cancer.gov	4 Feb 2011	medication: selenium indication: prevention	
Cancerlit	Oct 2004	1 selen* OR organoselen* OR natriumselen* 2 random* OR placebo* OR clinical trial* OR controlled trial* OR controlled clinical trial* OR double blind* OR single blind* 3 epidemiologic stud* OR cohort OR case-control stud* OR nested case-control* OR case-control design* OR prospectiv* 4 2 OR 3 5 1 AND 4	Now included in MEDLINE database
Clinical Contents in Medicine (CCMed)	4 Feb 2011	selen* OR organoselen* OR natriumselen*	
CENTRAL	2017, Issue 2	#1 MeSH descriptor: [Selenium] this term only #2 MeSH descriptor: [Selenium Compounds] explode all trees #3 MeSH descriptor: [Organoselenium Compounds] explode all trees #4 selen* #5 #1 or #2 or #3 or #4 #6 MeSH descriptor: [Neoplasms] explode all trees #7 (neoplasm* or cancer* or tumor* or tumour* or carcino* or malignan* or adenocarcinoma* or sarcoma* or adenoma* or chondrosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leiomyosarcoma* or liposarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma* or lymphoma*) #8 #6 or #7 #9 #5 and #8	
metaRegister of Controlled Trials (mRCT, www.controlled-trials.com)	4 Feb 2011	selen AND cancer	Now included in the ISRCTN registry
Embase Ovid	2017 week 6	1 selenium/ 2 selen*.mp. 3 selenium derivative/	

(Continued)

		4 methylseleninic acid/ 5 methylselenium.mp. 6 exp organoselenium derivative/ 7 1 or 2 or 3 or 4 or 5 or 6 8 exp neoplasm/ 9 (neoplasm* or cancer* or tumor* or tumour* or carcino* or malignan* or adenocarcinoma* or sarcoma* or adenoma* or chondrosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leiomyosarcoma* or liposarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma* or lymphoma*).mp. 10 8 or 9 11 7 and 10 12 exp clinical study/ 13 crossover procedure/ 14 double-blind procedure/ 15 single-blind procedure/ 16 cohort analysis/ 17 observational study/ 18 (random* or factorial* or crossover* or cross-over* or cross over* or placebo* or (double adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer* or observ* or cohort* or prospectiv* or (case* and control*)).mp. 19 12 or 13 or 14 or 15 or 16 or 17 or 18 20 11 and 19 21 (exp animal/ or nonhuman/ or exp animal experiment/) not human/ 22 20 not 21 key: [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
German Cancer Study Register: www.studien.de	Feb 2017	selen
MEDLINE (via Ovid)	Jan 2017, week 4	1 Selenium/ 2 exp Selenium Compounds/ 3 exp Organoselenium Compounds/ 4 selen*.mp. 5 1 or 2 or 3 or 4

(Continued)

6 exp Neoplasms/

7 (neoplasm* or cancer* or tumor* or tumour* or carcino* or malignan* or adenocarcinoma* or sarcoma* or adenoma* or chondrosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leiomyosarcoma* or liposarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma* or lymphoma*).mp.

8 6 or 7

9 5 and 8

10 randomized controlled trial.pt.

11 controlled clinical trial.pt.

12 randomized.ab.

13 placebo.ab.

14 drug therapy.fs.

15 randomly.ab.

16 trial.ab.

17 groups.ab.

18 exp case-control studies/

19 exp Cohort Studies/

20 (cohort* or observ* or prospectiv* or (case* and control*)).mp.

21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22 9 and 21

23 exp animals/ not humans.sh.

24 22 not 23

key:

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier

pt=publication type

ab=abstract

fs=floating subheading

SIGLE	Oct 2004	?selen?	database discontinued in 2005
ISRCTN Registry (www.isrctn.com)	Feb 2017	selen AND cancer	

(Continued)

ClinicalTrials.gov Registry (www.clinicaltrials.gov)	Feb 2017	selen AND cancer

Appendix 2. Newcastle-Ottawa Scale for Cohort Studies

((*) means that a 'star' was assigned to the study for the corresponding item)

1) Selection

1.1) representativeness of the exposed cohort
a) truly representative of the average _____ (target population) in the community (*)
b) somewhat representative of the average _____ (target population) in the community (*)
c) selected group of users, e.g., volunteers / nurses
d) no description of the derivation of the cohort
1.2) selection of the non-exposed cohort
a) drawn from the same community as the exposed cohort (*)
b) drawn from a different source
c) no description
1.3) ascertainment of selenium exposure
a) secure record (biochemical records) (*)
b) structured interview (*)
c) written self report or medical record only
d) no description
1.4) demonstration that outcome of interest was not present at start of study
a) no history of disease or exclusion of cases that occurred in the first 12 months (*)
b) not stated

2) Comparability

2.1.) comparability of cohorts on the basis of the design or analysis
a) study controls for AGE (*)
b) study controls for SMOKING (*)

3) Outcome

3.1) assessment of outcome
a) independent blind validation (> 1 person/record/time/process to extract information or reference to primary source such as X-rays/ hospital records) (*)
b) record linkage (e.g., ICD codes in databases) (*)
c) self report
d) no description
3.2) Was follow-up long enough for outcomes to occur?
a) yes (> 3 years)
b) no
3.3) adequacy of follow up of cohorts
a) complete follow-up of all subjects (*)
OR
b) subjects lost to follow-up unlikely to introduce bias (< 5% lost to follow-up or description provided of lost people) (*)
c) follow-up-rate < 95% and no description of those lost
d) no statement

Appendix 3. Additional Newcastle-Ottawa Scale for Nested Case-Control Studies

((*) means that a 'star' was assigned to the study for the corresponding item)

1) Selection

1.1) case definition
a) independent validation (> 1 person/record/time/process to extract information or reference to primary source such as X-rays/hospital records) (*)
b) record linkage (e.g., ICD codes in databases) or self-report with no reference to primary record
c) no description
1.2) representativeness of cases:
a) all eligible cases with outcome of interest over a defined period, cases in a defined catchment area/hospital etc. or an appropriate/random sample of those cases (*)
b) not satisfying requirements in part (a) or not stated
1.3) selection of controls:
a) community controls (same community and would be cases if had outcome) (*)
b) hospital controls (within the same population e.g., city as cases)
c) no description
1.4) definition of controls
a) cases had no history of outcome controls had no history of outcome OR case had new (not necessarily first) occurrence of outcome controls with previous occurrence of outcome should not be excluded (*)
b) no mention of history of outcome

2) Comparability

(validated in cohort assessment in question 2 - number of stars was copied)

3) Exposure

3.1) ascertainment of selenium exposure:
(validated in cohort assessment in question 1.3 - number of stars was copied)
3.2) Same method of ascertainment for cases and controls
a) yes (*)
b) no
3.3) non-response rate
a) same rate for both groups (*)
b) non-respondents described
c) rate different and no designation

F E E D B A C K

Selenium for preventing cancer, 23 November 2011

Summary

Re: Dennert et al., Selenium for preventing cancer, *The Cochrane Library*, 2011, Issue 5. As selenium scientists with considerable knowledge of the selenium-cancer field, we wish to draw to the attention of The Cochrane Collaboration the shortcomings of the recent review cited above. We contend that the quality of this review is not up to the expected standard of Cochrane systematic reviews.

We are not criticising the way in which the analyses were performed, but rather the ways they were interpreted and summarised, which we believe to be overly negative and rather biased. For these reasons, we find the resulting report to be misleading to the reader. Some of the weaknesses are listed below.

Abstract and Plain Language Summary:
These sections do not fairly represent the findings of the review. Contrary to the impression given in these summaries, the review itself demonstrates that there is in fact a considerable body of evidence, much of it from prospective observational studies, for a beneficial effect of selenium on a number of cancers. The stated summary of RCT findings is more conclusive than it should be, given the very small number of published clinical trials with selenium alone and the limited trial data that the review authors arbitrarily chose to consider. Furthermore, the NPCT is treated very harshly, and its secondary findings (lung, colorectal and prostate cancers) are more or less discounted.

Body of the Paper:
1. Lack of appreciation of the importance of baseline selenium status in influencing trial outcomes (i.e. the fact that only people with a low selenium status profited from supplementation). For example, no acknowledgement was made of the fact that lack of benefit of a 200 µg/d dose of selenium for cancer risk in SELECT occurred in participants with relatively high baseline serum selenium concentrations—well above those found to confer benefit from selenium supplementation in the NPC trial (NPCT). This point was raised by us previously (Rayman et al. JAMA 2010).
2. Lack of discrimination between trials in which supplementation with selenium had the capacity to maximise selenoprotein expression/concentration (e.g., NPCT) and those (e.g., SELECT) in which selenoprotein expression/concentration would already have been maximised at baseline.

3. Lack of appreciation that, despite the high selenium status of SELECT men, the effects of selenium supplementation on type 2 diabetes risk were not significant.
4. Failure to understand that biomarkers of selenium status are considerably more reliable than dietary data, which we know to be much more error-prone.
5. Frequent failure to distinguish between significant and non-significant findings.
6. Lack of familiarity with the relevant selenium literature.
7. No mention of oesophageal or gastric cardia cancer results (although RCT results for these are not based on selenium alone) and, in relation to colorectal cancer, no mention of adenoma data.
8. In 'Implications for research', no mention is made of the need to carry out randomised controlled trials in low-selenium populations, nor to take into consideration selenoprotein genotype, which has been shown to affect selenium metabolism. The relevance of the species of selenium administered in various trials is not mentioned.

Reply

The authors wish to thank the colleagues Doctors Brigelius-Flohé, Combs, Davis, Green, Hesketh, Köhrle, Kristal, Rayman, Schomburg, Taylor, van den Brandt, Waters and Whanger for their detailed commentary on the selenium review.

Their comments captured some of the same concerns that we had regarding the methodological challenges associated with conducting a systematic review in the field of selenium and cancer.

In response to the commentary, we will first address concerns related to the specific setting of this review as a Cochrane review and will then respond to concerns regarding the content of the review.

We strongly agree with the concerns that it is difficult to capture all differentiations elaborated on by the review in the abstract and summary, which are limited to a certain length. Similarly, length limitations were applied to the background section. We also share the opinion that some headings in the review do not adequately reflect the content of the text that follows. For readers who have not authored Cochrane reviews themselves, we wish to explain that Cochrane reviews are submitted in an electronic format that does not allow for all adaptations authors might wish to make. The headings, for example, cannot be changed. This electronic format is optimised for reviews on intervention studies. Our review included both RCTs and epidemiological studies, and so we encountered several structural challenges throughout the review process. We hope that both the commentary of our colleagues and our experiences will contribute to the continuing work of advancing the structural processes of The Cochrane Collaboration, including the electronic software Review Manager, and to developing a more inclusive format for reviews, which encompasses epidemiological studies.

Has the condensation of information in the abstract and the plain text summary led to a distortion in the presentation of the review results?

The abstract and the plain text summary present to readers the body of evidence that was reviewed as the main results for both study questions. Our aim was to report the answers to our research questions, and although space was a limitation for the abstract and summary results sections, we have endeavoured to provide across the entire review all the best available evidence for the role of selenium in preventing cancer.

We agree with our colleagues that no studies can be found on the association of selenium with cancer in children or on the preventive efficacy of selenium supplements in children. Hence, as stated in the abstract, there is currently no convincing evidence that selenium supplementation may prevent cancer in children. However, we are completely happy not to mention children in the abstract if this may be considered misleading.

We agree with our colleagues that long-term supplementation is more likely than short-term supplementation to influence cancer risk, if any effect exists. The minimum of four weeks has been chosen arbitrarily. However, no consistent current agreement has indicated where to draw the line between short-term and long-term selenium supplementation, so any cutoff would be arbitrary to some extent. In addition, we wished to avoid making assumptions about supplementation effects in our inclusion criteria and decided rather to address the question of the effect of shorter supplementation periods in the review discussion, if any trial would have been identified.

To our knowledge, there is currently no universal recommended daily allowance for selenium intake or upper tolerable level; therefore recommending a selenium dose or level of safe intake would not be appropriate in this instance. This is clearly an area for further research, taking into account some of the potential influencing factors cited in our review (e.g., baseline levels, gender, population, source). We would like to thank the commentators for the hint to the RNI (reference nutrient intake) values for selenium in the UK, which we are happy to include in a future update of the review. Nevertheless, regarding the RNI, we would like to draw attention to the latest draft of a position paper on selenium by the Scientific Advisory Committee on Nutrition (2011), which notes “that the selenium dietary reference value was set on very limited data and could be set too high” (p74).

Dr Brigelius-Flohé and colleagues commented that “Quoted recommendations such as 30 and 40 µg/d for men and women (WHO 2004) are no longer credible to anyone with up-to-date knowledge of the endpoints and biomarkers (SePP, GPx activity) that we have in 2011. There is no justification for quoting the Vinceti 2009a opinion that 20 µg/day organic selenium should be the maximum safe level.”

The suggestion of an upper safe limit of organic selenium of 20 µg/d was made by Vinceti et al. on the basis of preliminary results of the ORDET study (Vinceti 2009b), published in 2010 (Stranges 2010), and of other studies (please see for a review Vinceti 2009a). The recent

availability of new data on endocrine (Lippman 2009; Stranges 2007) and dermatological (Lippman 2009) toxicity of low doses of organic selenium adds new findings supporting the recommendations by the WHO Group. We would like to draw attention to other recent studies on selenium toxicity (reviewed by Vinceti 2009a and Nogueira/Rocha 2011) and the issue of risk assessment of selenium (including the use of uncertainty factors (UF) or alternative approaches) (Aggett 2010; Douron 2010; Renwick 2006; Renwick/Walker 2008).

The diverse recommendations and the controversial discussions clearly underline the need for a systematic review in this field.

To address our research question—What evidence exists on the efficacy of selenium supplementation for cancer prevention?—we restricted our focus to RCTs with mono-selenium supplementation. Multicomponent interventions, such as those chosen in the SU.VI.MAX, involve several nutritional/antioxidant supplements (e.g., 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium, and 20 mg of zinc in SU.VI.MAX), some of which are reportedly thought to have a potentially synergistic effect with selenium (Willett 1983); others may act as antagonists (Schrauzer/White/Schneider 1977) or may have an unknown biological interaction. Although all these factors are important considerations for the overall efficacy of selenium in the long term, we thought that inclusion of these studies in attempts to elucidate an actual anticarcinogenic role for selenium in its own right could potentially conceal the true effects (positive or negative) of selenium. By including the four studies that were mentioned in the commentary, which used multicomponent interventions, we may have gained numbers but lost out in trying to elucidate the actual effects of selenium. Therefore, these RCTs, which use selenium in combination with other nutritional factors, were outside the scope of the current review process but have been addressed in the background and discussions and could be the focus of future valuable investigations.

To avoid any potential preferential and non-systematic selection of studies and hence results, we established a set of *a priori* inclusion criteria during the initial stages of the study design. These were outlined in the protocol of the review, which has been available on *The Cochrane Library* website and for comment since 2005.

The details of all selenium supplementation have been reported for each RCT, including the form of selenium when available, and we emphasised the importance of carefully evaluating the different biological activity and toxicity of each selenium compound. Please refer to the plain language summary: “In general there are two types of selenium supplements: one type uses the salt of selenium as the main ingredient, the other type uses organic selenium. These two types may act differently in the human body when ingested,” and in the RCTs and preventive efficacy section: “Interpretation of the results of clinical trials using selenium supplements should consider the different biological forms as well as their potential differential health effects when supplemented”; and please refer to the table Characteristics of included studies, for details on each RCT.

References are made throughout the review text to the baseline selenium status of study participants and potential interactions with study results. Please refer to Section 2.3. Adverse effects, “The RR for developing type II diabetes mellitus was higher in the participants in the upper two tertiles of plasma selenium levels, indicating a possible interaction with baseline exposure status”, for instance, or page 38 in our review: “SELECT participants had a higher selenium level at randomisation than men in the NPCT. While the mean plasma selenium concentration was 113 to 114 µg/L in the NPCT, median serum concentration was 135 to 138 µg/L in the different study arms in SELECT. Lower prostate cancer incidence in the NPCT trial was confined to men with baseline selenium levels in the lower two thirds (below 121 µg/L). Subgroup analyses of the SELECT trial are underway to investigate a possible modification by pre-intervention selenium levels“.

Regarding the findings of NPCT and SELECT for type 2 diabetes, we would like to refer our readers to Section 2.3. Adverse effects, “A statistically non-significant increase in diabetes mellitus type II in the selenium-alone group (HR 1.07 (99% CI 0.94: 1.22)) was seen. An increased risk for diabetes mellitus type II was also observed in the NPCT (Stranges 2007, in: NPCT 1996). A secondary analysis of participants who did not have diabetes at start of the study revealed an excess risk in the selenium group (adjusted HR 1.55 (95% CI 1.03 to 2.33))”. We have previously outlined the section that referred to the fact that selenium baseline levels were higher in this group and would like to cite the original paper by Stranges et al. (2007), which stated: “Despite the lack of statistically significant interactions between treatment group and baseline co-variates, the risk for type 2 diabetes was consistently higher in the selenium group within all subgroups of baseline age, sex, smoking

status, and BMI.” (p220). Regarding the issue of a potential diabetogenic effect of selenium supplements and gender, we would like to draw attention to a recent observational cohort study by Stranges (2010), which documented an excess risk of diabetes among a large cohort of women from Varese, Northern Italy. Such a diabetogenic effect of selenium is also supported by suggestive laboratory evidence, recently reviewed by Steinbrenner al. (2011).

Lippman et al. (2009) stated in their publication about the SELECT trial: “The data and safety monitoring committee had some concern over the statistically non-significant increase in prostate cancer in the vitamin E-alone group (*P*=.09 per interim data of August 1, 2008) and over a non-significant increase in diabetes mellitus associated with selenium (*P*=.08 per interim data of August 1, 2008)” (p45).

The observation from SELECT (Klein 2011) that the effect diminished over time may suggest exactly the opposite to that hypothesised by Dr Brigelius-Flohé and colleagues. A decrease in the diabetogenic effect of selenium administration over time after interruption of such administration may well indicate a decreasing adverse effect over time, as expected, of a causal association. This was what occurred in the SU.VI.MAX study, in which administration of selenium/vitamins C-E/beta-carotene/zinc led to an excess incidence of skin cancer, including melanoma (Hercberg 2004), which entirely disappeared after interruption of the intervention (Ezzedine 2010). The investigators interpreted such decreasing risk as an indication of the causal effect of the treatment of skin cancer and the origin of melanoma (Ezzedine 2010).

Regarding the interaction of baseline PSA levels with selenium effects in the NPCT, we would like to quote the original publication: “The protective effect of SS [selenium supplements; GD] appeared to be confined to those with a baseline PSA level of <= 4 ng/mL (0.35, 0.13–0.87), although the interaction of baseline PSA and treatment was not statistically significant“ (p608, Duffield-Lillico 2003a). To summarise, no statistically significant interaction was noted between baseline PSA levels and prostate cancer incidence, as reported by the study authors.

Dr Brigelius-Flohé highlighted a sentence on page 4 that might be misunderstood if taken out of its context (“risk ratios (RRs) with confidence intervals (CIs) were not calculated because of low numbers”). Our colleagues rightly stated that Hercberg et al. (2004) provided hazard ratios for cancer incidence by gender. However, the sentence our colleagues quoted from our review reads in the context as follows: “In the more recent French SU.VI.M.AX trial (Hercberg 2004), a supplementation with beta-carotene, vitamin C, vitamin E and 100 µg selenium-enriched yeast did not alter the incidence of cancer of the digestive tract after a median period of 7.5 years in women. In men, the incidence rate was lower in the intervention group than in the placebo group, but risk ratios (RRs) with confidence intervals (CIs) were not calculated because of low numbers”. The part of the sentence our colleagues cited about the men’s incidence rate refers to cancer of the digestive tract. Site-specific cancer rates were not calculated or reported by gender: “We were not able to ana lyze differences in site-specific cancers between men and women because of low statistical power” (p2340, Hercberg 2004).

Our colleagues highlighted another sentence on page 39: “Results from two randomised controlled trials (NPCT and SELECT) have failed to provide evidence that non-melanoma skin cancer or prostate cancer can be prevented by selenium supplementation in men”. This statement refers to the primary study outcomes of both investigations, which were non-melanoma skin cancer in NPCT and prostate cancer in SELECT, and is correct. Contrary to what was stated by Dr Brigelius-Flohé and colleagues, the outcome measures in the NPCT were incident basal cell carcinomas and squamous cell carcinomas, and recurrent skin tumours were excluded from analysis, as summarised in the report of the primary NPCT endpoint by Duffield-Lillico et al. (2003b). We clearly stated in our review that the NPCT was carried out among non-melanoma skin cancer participants at baseline.

Our conclusions have been based on the available evidence, and we have highlighted the paucity of literature and data available from RCTs. Please refer to the 'Implications for research' section: “Potential differential effects of sex/gender and the use of selenium supplements in populations with a high burden of specific types of cancer diseases and differing selenium exposure levels, e.g., known low nutritional selenium intake, require further examination”.

Dr Brigelius-Flohé and colleagues have also expressed concerns regarding our inclusion criteria for epidemiological studies and the ways results of epidemiological studies were included and presented in the systematic review.

In reply to their concern, we might have omitted three relevant studies for gastrointestinal cancers; we would like to refer them to the detailed references to both studies, Mark 2000 and Wei 2004, throughout the review. The Steevens (2010) study has not been included, as it was not available at the time of our review process and submission to The Cochrane Collaboration Group (please refer to Methods section, Search strategy). As reported in Section 1.1.6 of the review, the strength of association varied according to what was included in analyses (e.g., cardia vs non-cardia cancers, gender), thus preventing any clear and concise conclusion to be drawn between selenium levels and upper gastrointestinal cancers in the observational summary results.

As we understood the publications Wei 2004 and Mark 2000, Wei 2004 reports on a population that was part of the population at risk in Mark 2000. Participants in Wei 2004 were the disease-free controls for the cases of Mark 2000. Because of this overlap, we decided to report the papers jointly and put emphasis on the detailed description of both papers and their study populations (please refer to the Characteristics of included studies).

Dr Brigelius-Flohé and colleagues criticised inclusion in the review of observational studies assessing selenium exposure as intake (e.g., with food frequency questionnaires).

Regarding the problems associated with dietary assessment, please refer to the section 'Bias and confounding': “Assessment of total selenium intake from food-frequency questionnaires (FFQ) or interviews has proven difficult in other investigations because of the lack of food composition data which adequately reflects regional and seasonal variations in selenium concentration”. Additionally, “The FFQ overestimated the mean selenium intake in study participants when compared with laboratory analyses of duplicate meals” and ”Validity problems, possibly leading to misclassification, have also been reported when questionnaires are used to assess supplement use”.

However, studies using dietary assessment add a valuable perspective to the discussion of the relationship between selenium exposure and cancer risk. Furthermore, in addition to the literature cited by Dr Brigelius-Flohé, other studies (van den Brandt PA et al, 1993; Longnecker et al., 1996; Haldimann et al., 1996) have reported a direct correlation between dietary and body selenium (please also see for a review of this topic Vinceti et al. 2000b and Vinceti et al. in press).

We consider the issue of selenium exposure assessment to be more complex than has been implicated by our colleagues´ comments. Assessment of selenium intake, despite the difficulties associated with its variability and possible individual variability in absorption, in some cases might even yield better estimates of actual exposure compared with biomarkers. This adds an important perspective to the discussion of why several observational studies have suggested a protective effect of higher selenium exposure towards cancer risk and others have not.

With regard to toxicity, animal studies have demonstrated that the intake of equivalent amounts of selenium, when administered in different species, might induce a stronger effect even when retained to a lesser extent (Panter et al., 1996), as shown for the inorganic compounds. The wealth of toxicological data from laboratory studies is clearly and, for obvious ethical reasons, much greater than those yielded by human studies. The same is true for studies investigating tissue distribution and biological activity of the different selenium compounds (see: Hatfield/Berry/Gladyshev 2012). We consider references to laboratory and animal studies as a necessary and valuable contribution to the understanding of selenium effects in humans.

Dr Brigelius-Flohé and colleagues asked why our summary of the findings of the review of Ashton (2009) on the use of biomarkers for selenium measurement did not mention singular nucleotide polymorphisms (p34 in our review). We summarised the findings of Ashton 2009 that were relevant for the discussion of bias and confounding in our review. Genetic polymorphisms were not included in the analyses of heterogeneity between study results by Ashton (2009). Instead, Ashton et al. proposed singular nucleotide polymorphisms in their discussion as an area for future research and stated: “Also, for all potential biomarkers, more information is needed to understand the limitations of applicability for different population groups, the possible effects of genotype, supplementation doses, duration, baseline status, etc” (p2037S).

The criticism that we failed to distinguish between significant and non-significant findings in epidemiological studies points to a fundamental difference in the interpretation of epidemiological study results. Indeed, we consider ‘statistical’ significance as an inappropriate approach to data analysis and interpretation with regard to observational studies, as has been long recognised (Rothman KJ 1978; Sterne/Davey Smith 2001; Greenland 2011), with no connection with ‘biological significance’. Pitfalls of statistical significance testing encompass dismissing so called `non-significant values´ in small studies or putting undue emphasis on ‘statistically significant’ results without attempting to integrate potential biases for a study finding that would affect the estimates from that study (see: e.g., Rothman, Greenland & Lash 2008; Stang/Poole/Kuss 2010). This may lead to confusion between the validity of an investigation and its statistical stability.

Analysis and interpretation of results in biomedical research must be based on a number of considerations, comprising both study design and data analysis. We made a conscious effort in our selenium review to avoid use of an approach that dichotomised study results according to which were statistically significant and which were not. We consider this effort a major strength of our review.

We have attempted to be prudent with our conclusions by highlighting important considerations associated with the results of epidemiological studies that we reported. Both the current literature and our review indicate that although some associations have been noted between selenium levels and risk of cancer at certain body sites (e.g., prostate, bladder), more research and information are clearly required before it can be concluded that these results are “convincing” for a protective effect of selenium. The World Cancer Research Fund’s Second Expert Report (2007) also suggests the possibility of residual confounding between selenium levels and healthy lifestyles (p109).

We admit that the sentence about the marketing situation of selenium in our discussion section expresses a valuation, and we acknowledge that other colleagues might assess the marketing situation differently and as such might disagree with this sentence.

In the last part of our reply, we will address the concerns by Dr Brigelius-Flohé and colleagues regarding the content of the background section of the review.

The reference Rodriguez 1995, which is listed in the MEDLINE database, in contrast to what our colleagues stated (please refer to PubMed ID 7605824), is an early study that investigated urinary selenium in healthy men and women and addressed the study question of the relationship between factors such as gender/sex, etc., and urinary selenium. It found gender/sex differences in urinary selenium excretion, as well as influences of health behaviours (physical activity), as stated in our background text.

We do not agree that studies investigating primarily the relationship between selenium status, thyroid volume and gland echostructure (Derumeaux 2003) or the relationship between baseline plasma selenium concentration and occurrence of dysglycaemia (Akbaraly 2010) would have been more suitable references for the statement that we made regarding gender differences.

We also would like to recapitulate the Vinceti et al. (2000a) paper because we feel that Dr Brigelius-Flohé and colleagues misreported the methods and findings of this study. The Vinceti et al. studies in an unusual Northern Italy setting evaluated the health effects of selenium in its inorganic hexavalent form—the one usually found in underground and drinking water—together with the tetravalent species (Vinceti 2010). This study was a ‘natural experiment’, considered to be ‘the paradigm of non-experimental epidemiologic research’, as in this type of study, ‘nature emulates the sort of experiment the investigator might have conducted, but for ethical and cost constraints’ (p94, Rothman/Greenland/Lash 2008). Study authors assessed the potential for confounding by lifestyle by assessing the socioeconomic status of exposed and unexposed cohorts, and labelling this study as a natural experiment was allowed only after the similarity of the two populations was confirmed. Dr Brigelius-Flohé stated that Vinceti et al. admitted that their results are consistent with “no effect”, as standardised mortality ratios were generally inconsistent between men and women at most sites, and most site-specific estimates had limited precision. The citation in the original publication reads: “The results of our study are consistent with either no effect or, particularly among the elderly, unfavourable effects of long-term exposure to inorganic selenium on cancer mortality”. Then Vinceti et al. analysed the strengths and limitations of their study, both for the melanoma association and more generally for the effects on cancer risk. Excess melanoma risk, despite different study designs and strengths of association, has been documented to be associated with selenium exposure in a number of studies (Garland 1995; Vinceti 1998; Duffield-Lillico 2002; Vinceti et al., in press) and has been causally associated with administration of

selenium in combination with zinc and vitamins in SU.VI.MAX (Hercberg 2007). In general, we would like to propose caution when dealing with the possible selenium-melanoma association.

In conclusion, we express our appreciation to our commentators for scrutinising our review, offering their criticisms and supporting the scientific endeavour of enclosing epidemiological as well as intervention studies in a Cochrane review. We are hopeful that the review and the commentary of our colleagues will contribute to the important and continuing discussion about the health effects of selenium and selenium supplements globally and in diverse populations.

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Maree Brinkman, Gabriele Dennert and Marco Vinceti on behalf of the review authors.

Selenium for preventing cancer, 30 October 2014

Summary

Comment: Selenium for preventing cancer; The Cochrane Library 2014, Issue 3 Vinceti M, Dennert G, Crespi CM, Zwahlen M, Brinkman M, Zeegers MPA, Horneber M, D'Amico R, Del Giovane C

We are pleased to see that a revised version of the review has now been published though it has taken longer than we would have wished. In the updated review, the authors have remedied some of the shortcomings which we pointed out, but not all. I have attached detailed comments on what we think still needs to be changed and hope that these points can be remedied in the very near future.

Comments by section are given below.

Abstract

1. Selection criteria refer to including RCTs with "healthy adult participants". However, it is clear that SELECT was the only trial that included "healthy adult participants", all other trials included participants with a high risk of cancer (Li, Yu 1991, Yu 1997, Marshall, Algotar, Dreno) or a previous history of cancer (NPCT 2002, Reid 2008). The word "healthy" should be removed and the statement should be modified to reflect the high proportion of participants at high risk of cancer.

2. The main results of the pooled analysis of RCTs overwhelmingly reflect the results of by far the largest trial, SELECT. However, SELECT was carried out in a population of high selenium status. This needs to be mentioned either under "Main results" or under "Authors' conclusions". Not to mention it is to ignore a fact that is likely to be highly relevant to the outcome.

3. The "Authors' conclusions" assert that there is "little evidence of any influence of baseline selenium status", but that lack of evidence all relates to trials in populations of much higher baseline selenium status than the NPCT where such an effect was seen: baseline plasma Se was 114 µg/L in the NPCT compared to 126.1 µg/L in Algotar and 135.2-138.1 µg/L in Marshall. [No such effect was seen in SELECT, but baseline selenium status was also high - 136 µg/L (Kristal et al. 2014).]

Plain language summary
The sentence that begins "Recent trials that were judged to be well conducted and reliable… " should be modified to read "Recent trials that were judged to be well conducted and reliable, though conducted in high-selenium populations, have found no effects of selenium supplementation on reducing the overall risk of cancer or on reducing the risk of particular cancers, including prostate cancer".

Main text
Page 5 column 2: We previously pointed out that having inclusion criteria that allowed RCTs of only four-weeks' length to be included is unjustifiable. While no studies as short as that were included, clearly a four-week intervention with Se is insufficient to alter cancer risk so what is the justification retaining this inclusion criterion?

Page 21 column 1: We previously objected to the description of an increased risk of diabetes mellitus type 2 being found in SELECT yet such a description is there again: "An increase in diabetes mellitus type 2 was seen in the selenium-alone group (RR 1.07, 99% CI 0.94 to 1.22)", despite the confidence interval spanning 1. The only trial in which an increased risk of type-2 diabetes was seen was the NPCT. The authors also refer to a short-term effect of selenium supplementation on type-2 diabetes risk. However, there is no mention, either here or elsewhere, of our RCT that found no increased risk of type-2 diabetes in 500 people treated with 100, 200 or 300 µg selenium or placebo for a period of six months (Rayman et al. A randomised trial of selenium supplementation and risk of type-2 diabetes, as assessed by plasma adiponectin. PLoS One. 2012;7:e45269).

Page 20-21: There should have been some mention of baseline selenium status in this section. Clearly SELECT was showing evidence of toxicity, which is unsurprising given the high baseline status and substantial level of supplementation.

Page 23 column 2: In discussing the change from a protective to a possibly detrimental effect, the authors should be aware of the possibility of a threshold effect that may relate to a mechanism dependent on selenoprotein concentration/activity. Furthermore, discussing the relationship between selenium status and the risk of non-melanoma skin cancer and type-2 diabetes in the same breath ignores the likelihood of totally different mechanisms applying.

Page 23 column 2: The sentence "Little evidence of a beneficial effect of selenium supplementation was noted among participants with the lowest baseline selenium exposure (plasma selenium < 106 µg/L) in either the prostate cancer trial of Marshall et al. (Marshall 2011) or the prostate cancer trial of Algotar et al. (Algotar 2013), despite the fact that 45% of the participants in that study had baseline plasma selenium levels < 123 µg/L – the suggested threshold for beneficial effects of selenium supplementation according to the NPCT (NPCT 2002)", should be qualified by pointing out that both the Marshall and Algotar trials were in men at high risk for prostate cancer and in whom prostate cancer was probably already initiated. Thus this is not an appropriate test for evidence of benefit of selenium supplementation for primary prevention in those with low selenium status.

Page 24 column 2: SNPs could be mentioned as a potential explanation of "the … unexplained heterogeneity in the reaction of participants' plasma selenium levels to selenium supplementation".

Page 25 column 1: As explained in our criticisms of the primary review, we and others profoundly disagree with the statement that "measurements of nutritional intake might provide better exposure estimates than do biomarkers, which may considerably mis-classify the exposure to inorganic and organic selenium sources". This is particularly true of exposure to selenium where food concentration data differ very considerably from one part of the world to another and many countries have no such data.

Page 28 column 1: The paragraph that contains the sentence "These ideas stimulated the largest ever cancer prevention trial, SELECT, which failed to provide support for this hypothesis, and two additional prostate cancer trials (Algotar 2013; Marshall 2011),whose results were in line with the SELECT findings in failing to find a beneficial effect of selenium", needs to point out that SELECT, Algotar 2013 and Marshall 2011 were all carried out in high-selenium populations and that Algotar 2013 and Marshall 2011 were both in men at high risk of prostate cancer.

Page 29 column 2: It is not especially accurate or informative to say that the Blot and Hercberg trials produced divergent results. Although they were both RCTs, they used very different designs in hugely different populations with different baseline selenium levels. It could equally fairly be said that they produced comparable results in that they both saw beneficial effects (of one sort or another).

Page 30 column 1: Karp was a secondary prevention trial in lung-cancer patients. In relation to that trial, there should be some mention of the likely difference in mechanisms of primary prevention and those relevant to prevention of secondary tumours in already initiated patients.

Page 30 column 1: the previous RCT that found no increased risk of type-2 diabetes in 500 people treated with 100, 200 or 300 µg selenium or placebo for a period of six months should be mentioned (Rayman et al. A randomised trial of selenium supplementation and risk of type-2 diabetes, as assessed by plasma adiponectin. PLoS One. 2012;7:e45269).

Page 30 column 1: Under the heading, "Implications for practice", it should be made clear that the "Results from the most recent randomised controlled trials, which were carried out in men and had a low risk of bias" were all in men of high selenium status.

Page 30 column 2: Under "Implications for research", there is a statement that needs qualifying, "whether selenium might influence cancer risk in individuals with very low or very high baseline exposure to this element …….. have not been fully resolved, although currently available evidence from randomised trials offers little support for such hypotheses". It needs to be acknowledged that there are no cancer trials of selenium as a single nutrient in people with low baseline selenium status.

Even if the results of SELECT are expanded to look at other endpoints, they will still not apply to low-selenium populations and cannot compare truly low to higher levels; this also needs to be specified.

A question that remains ignored by this review, by design, is whether selenium in combination with other agents may be beneficial in cancer. This deserves some sort of comment under "Implications for research".

Errors
Page 4, column 2: Though we pointed out in our previous set of comments that SU.VI.M.AX was incorrect, it has not been corrected.

Page 6 column 2: 78.96 is described as the molecular weight of selenium; it should be atomic weight.

Page 28 column 2: we have previously pointed out that selenium supplement are not aggressively marketed to women with regard to breast cancer prevention and treatment.

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I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

21-1-2015

We wish to thank Dr. Brigelius-Flohé and colleagues for their interest in our Cochrane review on selenium for preventing cancer.

Before addressing the specific points in their letter, we would like to clarify that our publication Vinceti et al. 'Selenium for preventing cancer, Cochrane Database Syst Rev. 2014 Mar 30;3:CD005195' was not a revised version of the previous Cochrane but rather an update, taking into account the additional three years of scientific literature on the topic, according to standard procedures of the Cochrane Collaboration.

With regard to the use of the term 'healthy' in RCTs, we used the term 'healthy' adult participants to mean that the (adult) individuals enrolled in the studies were free at the beginning of the trial from the disease representing the primary outcome, an incident cancer, as required when we deal with primary prevention trials. Being at high, low or intermediate risk of cancer, or affected by any other disease, or previously affected by another cancer, was not considered to be an exclusion criteria and did not preclude the term 'healthy' with respect to the trial outcome(s), which in all cases consisted of the incidence of a primary cancer. In our review, we specifically listed in detail the enrolment criteria for the trials, and before performing the meta-analysis we excluded studies retrieved with our literature search that

were not based on healthy adults (397 studies removed – see Figure 1 of our review). Being 'totally' healthy– i.e., apparently free from any disease and at a low risk for cancer or other chronic disease, was not a selection criteria for any of the selenium (Se) trials, including SELECT itself (for example, we used the term 'apparently healthy men' for the SELECT population in page 23).

As noted by Brigelius-Flohé et al., the pooled analysis is obviously influenced by the largest trial, SELECT, and this is even more true when we limited the analysis, as recommended by the Cochrane review guidelines, to the trials at low risk of bias. SELECT has been of fundamental importance in selenium (Se) research for its large size, long follow-up, and broad range of outcomes, all of which are important for defining the so far uncertain relation between Se and primary prevention of cancer and the adverse health effects of the metalloid. Results from SELECT, which are continuing to emerge in the literature (Kristal et al., JNCI; Martinez et al., Cancer Prev Res; Albanes et al., Cancer Prev Res 2014), in addition to other recent relevant trials (Karp et al., 2013), have been systematically confirmed by all the high-quality, low-bias trials so far carried out (some of which could unfortunately not be included in our review, having been published after our literature search deadline), with the exception of the excess high-grade prostate cancer risk in the Se-supplemented individuals with the highest baseline selenium status recently reported in SELECT (Kristal et al., JNCI 2014), an unexpected and concerning finding so far not investigated in the other trials with the partial exception of Marshall et al. (Cancer Prev Res 2011).

Assuming that the SELECT population was a group with 'high Se status' while NPC subjects had a low Se status, and suggesting that their different results were likely due to this, as claimed by Brigelius-Flohé et al., is not well-founded. Defining a low-Se status and a high-Se status is very subjective and debatable, but whatever approach is chosen, no such difference between these two trial populations emerges. We would argue that the more important distinctions between the two trials are that one had low risk of bias and high statistical power (SELECT), while the other one had high risk of bias and much lower power (NPC). The two trials also used different Se preparations. In fact, if we estimate Se intake though its relation with serum/plasma level computed with the rule of thumb proposed by Haldimann et al. (J Trace Elem Med Biol 1996) in the 30-120 µg/l of plasma or serum Se, average baseline dietary exposure corresponding to their blood Se levels was around 90 µg/day for SELECT participants, and 76 for NPC subjects. If we compare these values to the Se recommended dietary intake (or comparable indexes defined as 'recommended intake level', 'dietary reference value', 'average nutrient requirement' etc.), both are well above these reference values for Se, whether using the 26-34 µg/day recommended intake of the World Health Organization and Food Agriculture Organization (WHO-FAO 2004), the 25-35 µg/day range of the Japanese Ministry of Health Labour and Welfare (2005), the 55 µg/day of the US Institute of Medicine and Food Nutrition Board (2000), the 70 µg/day of European Food Safety Authority (EFSA 2014) or the 55 µg/day of the Italian Human Nutrition Society (SINU, Milan 2014). For a comprehensive review of this issue we refer to among other sources the Eurreca database at www.eurreca.org, Cavellaars et al., Eur J Clin Nutr 2010, Vinceti et al. 2013 Sci Total Environ, and to the EFSA journal, 2014. Thus, according to all of these standards, both the SELECT and NPC populations should be defined as having a 'high Se status'. This would be further strengthened should we use the 110 µg/L serum Se cutpoint for Se toxicity (increased prevalence of depressive symptoms and higher levels of urinary 8-oxo-7,8-dihydroguanine) recently suggested by two observational studies (Galan-Chilet et al., Free Rad Biol Med 2014 and Conner et al., J Nutr 2014): according to such threshold values, all the RCTs included in our review including SELECT and NPC, with the exception of the Chinese ones, should be considered as carried out in populations with 'very high' Se status.

In our review, given the uncertainties and complexity of the issue, we consciously avoided labelling the populations in RCTs as low or high Se status, preferring instead to report baseline exposure levels and to use relative measures for their comparison (such as 'lower status', 'the lowest exposure category' instead of 'low Se status', and the converse for higher exposures). This was done particularly for the most influential studies in the review, the RCTs, to facilitate assessment of whether baseline Se exposure may influence the response to Se supplementation in terms of cancer risk and comparison of distributions of baseline Se exposure. We refer Brigelius-Flohé et al. to our analysis in the review (pages 22/24), which found the following points, among others: the marginal difference in intake of around 15 µg/day between the SELECT and NPC populations, in contrast with usual differences of Se intake at the population and the individual level, which span hundreds of micrograms; the occurrence of adverse effects even in the trials with the lowest baseline exposure level, such as the increased incidence of skin cancer in NPC and of type 2 diabetes in all trials which so far investigated this outcome; and the considerable overlap of Se exposure levels between the various RCTs. Finally, in our review we had to state that 'analyses stratified by baseline Se status are not available for SELECT: Such analyses would greatly help to elucidate this issue.' Fortunately, such evaluation (though so far only for prostate cancer) has been subsequently published (Kristal et al., JNCI 2014, and specifically its table 4). As it happens, their finding based on quintiles of baseline Se exposure is consistent with our previous assessment. In fact, the abstract of that paper reported that 'Se supplementation did not benefit men with low Se status but increased the risk of high-grade PCa among men with high Se status.'

When programming the update of this Cochrane review, we decided not to further restrict the inclusion criteria for studies compared with the 2011 review, but rather to relax them somewhat. For example, meta-analysis was carried out for site-specific cancer types when only 2 randomised trials were available. We even discussed whether to include trials reported only as abstracts and not *in extenso*, but decided against this due to lack of consensus, even though this precluded consideration of at least two possible relevant RCTs, the Karp et al. trial for prevention of second primary tumours in patients with resected lung cancer (Karp et al., J Clin Oncol 2010) and a trial on the risk of cancer in *BRCA1* carriers (Lubinski et al., Hered Cancer Clin Pract 2011). We agree with Dr. Brigelius-Flohé et al. that a trial with only 4 weeks of supplementation would be very unsatisfactory, even in case of 'mega-dose' Se administration, and such a dosage scheme would not have passed un-remarked upon in our literature review, had we found such a study.

As far as Brigelius-Flohé et al. comments about the excess diabetes incidence in SELECT among subjects allocated to Se administration, we are surprised to see this objection: reporting and commenting on the adverse effects of RCTs is mandatory according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT and Green S, Chapter 4 'Adverse effects') and more generally according

to ethical and scientific issues. We also note that Brigelius-Flohé et al. when commenting on the excess diabetes incidence rely entirely on statistical significance testing ('..despite the confidence interval spanning 1'), an approach generally considered to be inappropriate for evaluating findings from epidemiologic studies (Sterne and Davey Smith, BMJ 2001; Rothman, Greenland and Lash, Modern Epidemiology 2008; Stang, Poole and Kuss, Eur J Epidemiol 2010), especially for adverse effects that the studies were not necessarily powered to detect. The excess diabetes risk was one of the concerning findings yielded by SELECT (Vinceti et al., Rev Environ Health 2009), mirroring the observation of an increased diabetes incidence detected in the previous NPC trial (Stranges et al., 2007). We also noted that such excess risk was found in all four RCTs that investigated this outcome, and this was also supported by some biological plausibility, though we did not carry out an in-depth investigation of the diabetes & Se relation, for which we refer to recent literature (Steinbrenner 2013; Vinceti et al., J Trace Elem Med Biol 2015). Contrary to the claims of Brigelius-Flohé et al., we did not mention the 2012 Rayman et al. trial published in PLoS One for the obvious reason that it did not include cancer nor diabetes among the outcomes under investigation.

The comment by Brigelius-Flohé et al. stating that 'Clearly SELECT was showing evidence of toxicity, which is unsurprising given the high baseline Se status and substantial level of supplementation' is also unfounded. Being ourselves among the few investigators who have systematically reviewed the human health risks of chronic low-dose Se overexposure, (Vinceti et al., Rev Environ Health 2001 and 2009; Vinceti et al., Sci Total Environ 2013; Vinceti et al., Toxicol Lett 2014), we must point out that the upper limit of 'safe' Se exposure was and is set at a higher level than that of the SELECT study groups allocated to Se administration, i.e. at 400 µg/day (US Institute of Medicine 2000; World Health Organization Food Agriculture Organization 2004, and the Office of Dietary Supplements of the National Institute of Health accessed at ods.od.nih.gov/factsheets/Selenium-HealthProfessional/ on January 20, 2015).

Brigelius-Flohè et al. challenge discussing the excess risk of diabetes and of non-melanoma risk cancer 'in the same breath' since this would 'ignore the likelihood of totally different mechanisms'. This misrepresents the review, which makes no claim that risk of non-melanoma skin cancer and diabetes operate through the same mechanisms.

Brigelius-Flohè et al. state that the participants in the Marshall et al. and Algotar et al. studies were at high risk for prostate cancer (as we mentioned in our review) and that prostate cancer was probably already initiated in them. The participants in these trials were biopsy-negative for prostate cancer, and therefore the latter statement by Brigelius-Flohè et al. is speculation not supported by the available evidence. Contrary to the claims of Brigelius-Flohè et al., the Marshall et al. 2011 trial and the Algotar et al. 2013 trial were important, not only since they confirmed key results of SELECT trial, but also since they addressed the issue of influence of baseline Se status on the effect of Se supplementation on (prostate) cancer risk. We refer Brigelius-Flohè et al. to pages 23 and 24 of our review where we analysed this issue in-depth, and specifically to the following text: "Little evidence of a beneficial effect of Se supplementation was noted among participants with the lowest baseline Se exposure (plasma Se < 106 µg/L) in either the prostate cancer trial of Marshall et al. (Marshall 2011) or the prostate cancer trial of Algotar et al. (Algotar 2013), despite the fact that 45% of the participants in that study had baseline plasma Se levels < 123 µg/L-the suggested threshold for beneficial effects of Se supplementation according to the NPCT (NPCT 2002)". In addition, as previously mentioned, a 2014 report published after final submission of our review showed that SELECT subjects in the lowest baseline status categories did not benefit from Se supplementation with regard to (prostate) cancer risk, though they did not experience the increased risk of high-grade prostate cancer induced by the Se supplementation observed in the highest exposure groups (Kristal et al. JNCI 2014).

We did not mention SNPs as a potential explanation of "the ... unexplained heterogeneity in the reaction of participants" since we were specifically reporting the comments of Ashton et al. Am J Clin Nutr 2009, who did not primarily focus on this possibility. However, as Brigelius-Flohè et al. may note from several statements within our review, we agree about the potential importance of SNPs, and this is why we frequently mention the potential role of genetic factors in our review.

Page 25, column 1 (assessment of Se exposure): though we could not review in-depth all studies concerning methods for assessing Se exposure and related issues, we wanted to mention the human studies finding an association between dietary and biomarker Se, those unable to find it, and the advantages and limitations of all these approaches. We refer Brigelius-Flohè et al. to specific reviews or research papers on this important issue, which show that inadequate Se exposure classification made on the basis of dietary intake or of hair, blood, urine and toenail levels may have had a major role in the inconsistencies among various observational studies and between the observational and the experimental investigations. We stand behind the brief statement in our review concerning Se exposure assessment methods in the human body.

Contrary to the claims of Brigelius-Flohé et al., the Blot and Hercberg trials indeed produced divergent results, and the statement about these two trials that 'both saw beneficial effects' is untrue. Though the effects of these trials administering (different) mixtures of vitamins and minerals and carried out in very different populations cannot be adequately summarized in few words, it can be easily appreciated that the Chinese trial found beneficial effects on decreased mortality, mainly due to reduced cancer rates (especially for stomach cancer) (Blot et al., JNCI 1993 and Am J Clin Nutr 1995) while the second trial found beneficial, null and adverse effects of supplementation overall as well as specifically for cancer (Hercberg et al., Arch Intern Med 2004 and Br J Nutr 2006). Among the adverse effects following supplementation, Hercberg et al. found an alteration of the lipid profile (Hercberg et al., Lipids 2005) and an increase in melanoma incidence (Hercberg et al., J Nutr 2007), later shown to decrease during the post-intervention follow-up, further supporting a causative role of the treatment (Ezzedine et al., Eur J Cancer 2010). However, since these two trials did not include an intervention arm receiving Se alone, they were excluded from our meta-analysis as were all trials that administered Se together with other substances. They were included in a different Cochrane review (Bjelakovic et al. Cochrane Database Syst Rev 2012).

Page 30, column 1: contrary to the statements of Brigelius-Flohé et al., the Karp et al. trial, published *in extenso* in J Clin Oncol 2014, was not a secondary prevention trial, but a primary prevention trial, as we indicated in our review. As literally abstracted from the Karp paper, study objectives were "*to evaluate the efficacy of Se supplementation in reducing the incidence of lung second primary tumors in patients who had been treated for stage I non–small-cell lung cancer; to evaluate the qualitative and quantitative toxicity of daily Se supplementation; and to compare the incidence of specific cancers, mortality from cancer, and overall survival of patients treated with Se supplementation versus placebo*". The study population was therefore comparable to that of the NPC trial in the sense that both included participants with a recent history of cancer: the first trial comprised 1561 individuals who had been treated for stage I non–small-cell lung cancer with complete surgical resection, while the second RCT included 1312 individuals with a history of two or more basal cell carcinomas or one squamous cell carcinoma of the skin, with one of these occurring within the year prior to randomization. We note that the results of the low-bias Karp et al. trial, which could not be meta-analysed in our review having been published *in extenso* beyond the literature search deadline, were fully consistent with the conclusions of our review.

Brigelius-Flohé et al. state that 'A question that remains ignored by this review, by design, is whether Se in combination with other agents may be beneficial in cancer'. As they correctly recognize, this was not included among the objectives of our review. However, we agree with Brigelius-Flohé et al. concerning the use of selenium compounds in cancer therapy warranting strong attention and in-depth investigation, as stated in our section 'Se as a potential cancer therapeutic agent' in Vinceti et al., J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2013. However, caution must be used when addressing this issue, also due to the concerning results of a recent study in patients affected by nonmetastatic prostate cancer, where supplementation of ≥140 µg/day Se was found to be associated with excess mortality from prostate cancer (Kenfield et al., JNCI 2015).

We wish to thank Brigelius-Flohé et al. for their search for typos and mistakes in our 193 page review. They claim that three errors were found; however, these were not errors. The acronym SU.VI.M.AX was sometimes used by the authors of that trial, and we used it in our review only when citing a reference titled with that form of the acronym (Arnaud et al., J Trace Elem Med Biol 2007), while we used the more common 'SU.VI.MAX' for the remaining papers. As far as the 78.96 'molecular weight' of Se is concerned, we recognize that the adjective 'atomic' is more commonly used than 'molecular', but the latter may also be used in connection with 'weight' for Se, as it may be observed at the PubChem Open Chemistry database of the US National Institute of Health (http://pubchem.ncbi.nlm.nih.gov/compound/Se, accessed January 20, 2015) or the US Center for Disease Control and Prevention - National Institute for Occupational Safety and Health website (http://www.cdc.gov/niosh/docs/81-123/pdfs/0550.pdf, accessed January 20, 2015). Finally, aggressive marketing of Se supplements for breast cancer can be detected through a simple Google Internet search. Admittedly, this is also true for other cancers, including of course prostate cancer, and more generally for chronic disease or conditions claimed to be due to oxidative stress and alleged to be prevented by Se. However, such marketing approaches differed depending on the diseases, populations, sources of information, strategies, and periods involved, and were not analysed because they were outside the scope of our current review.

Contributors

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Further discussion on 'Selenium for preventing cancer'

Summary

We are pleased with your positive response to our concerns and the expressed willingness of the review authors to make changes as appropriate. In particular, we welcome the following proposed modifications.

- A more accurate (and longer) abstract and plain language summary to take account of the concerns we specified in our letter and in the first of our "General criticisms".
- Modification of the review by ensuring that differences in baseline selenium exposure between trials are clarified and placed in the proper context.
- More careful use of language in relation to statistical significance, as, for instance, in the two examples you cite in your letter. The preferred form you quote is much better than the misleading use of "lower" or "higher" for "non-significant" effects, as occurred frequently in the review.
- Removal of constraints on the use of section headings so that more appropriate headings can be used.

There is little point in revisiting all of our criticisms as they were clearly set out in our original letter and document, and most still stand. We would like to see the review amended as soon as possible to take account of those criticisms and specifically to correct the inaccuracies that we have noted. The review authors have replied with a number of points that we would like to challenge.

- p2: *Re* the suggestion of an upper safe limit of organic selenium of 20 µg/d by Vinceti et al., the authors now justify the original inclusion of that statement on the basis of a study (ORDET) based on a semiquantitative FFQ at baseline and follow-up for development of type 2 diabetes 16 years later. Based on that same study (p4), the authors refer to "Such a diabetogenic effect of selenium…". A prospective study, especially one with a very weak study design such as ORDET, can only show an association—hardly a good basis for making such a statement in a Cochrane review. Furthermore, an upper safe limit of organic selenium of 20 µg/d would be just above that at which Keshan disease is seen—11 µg/d in a Chinese man, which translates to 14 µg/d in a man of Western body weight.[1]

- p2: The authors say, “The recent availability of new data about endocrine (Lippman 2009; Stranges 2007) and dermatologic (Lippman 2009) toxicity of low doses of organic selenium adds new findings which support the recommendations by the WHO group.” The authors seem still not to have taken on board the fact that Lippman et al. 2009 does*not* show any endocrine toxicity of selenium. Furthermore, the dose given—200 µg/d—was not low.
- p4: Diminution of the effect on type 2 diabetes over time. Proper interpretation of SELECT is that there was a null result during the trial (RR 1.07, P value 0.16) and a similarly null result with postintervention follow-up time included (RR 1.04, P value 0.34). If trial-only data versus post-trial-only data were compared, it is probably unlikely that there would be any difference statistically. However, we do understand the point the review authors make: Interpretation depends on how one thinks selenium acts. If we were talking about an effect that occurred immediately after starting a drug (e.g. platelet effect of aspirin, blood pressure reduction from antihypertensive) and stopped more or less immediately after cessation of the drug, then the review authors’ interpretation would have better credibility.
- In contrast to the week or so that the effect of aspirin on platelets lasts, selenomethionine has a long half-life of 252 d [363 d (turnover time) × 0.693 (from kinetic modelling)] (Swanson et al. AJCN 1991, 54:917-26). In medicine, when calculating dosing intervals for drugs, it is typical to give doses every five to six half-lives. When first-order kinetics is applied, five half-lives for total body selenium is 1260 days (3.45 years), and six half-lives is 1512 days (4.14 years). Although it is true that the amount of the original dose still remaining is small after five (6.25%) or six (3.13%) half-lives, excess residual selenium remains from the supplementation. So, on the basis of both observed effects with cancer and pharmacokinetic data, the events that occurred in the post-trial period for SELECT participants (34 additional months) should still be considered a period of selenium exposure and therefore incompatible with the review authors’ hypothesis.
- p6: We hotly dispute the assertion of the review authors (none of whom is a nutritionist) that “The assessment of selenium intake, despite the difficulties associated to its variability and the possible individual variability in absorption, in some cases might even yield better estimates of actual exposure compared with biomarkers”.
- p7: Gender differences: The Schomburg references would have been preferable; Schomburg is the accepted authority in this area.

We very much hope that our original comments and those contained in this letter will help the review authors, guided by the editors, to revise the review, so that it sits more comfortably with the opinion of experienced investigators in the selenium-cancer field.

Yours sincerely,

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Professor David J Waters, Purdue University, USA
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[1] National Academy of Sciences, Institute of Medicine’s Food and Nutrition Board, Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids.
http://fnic.nal.usda.gov/nal_display/index.php?
info_center=4&tax_level=4&tax_subject=256&topic_id=1342&level3_id=5141&level4_id=10591.

Reply

We would like to thank Drs Brigelius-Flohé and colleagues for their continuing interest in our research activity on selenium.

We decided to shortly respond to some of their discussion points (citations from Dr Brigelius-Flohé et al are provided in italics):

- *“more careful use of language in relation to statistical significance as, for instance, in the two examples you cite in your letter. The preferred form you quote is much better than the misleading use of “lower” or “higher” for “non-significant” effects as occurred frequently in the review”*

Dr Brigelius-Flohé and colleagues do not acknowledge the limitations of their approach based on ‘statistical significance’ (please refer to the references provided in our previous reply). Their approach appears to have had major consequences for a number of considerations and statements in their two letters. It is of interest to note that even the SELECT “Data and Safety Monitoring Committee” expressed its concern “over a non-significant increase in diabetes mellitus associated with selenium (P = 0.08 per interim data of August 1, 2008)” (cited from Lippman et al., JAMA 2009), which we consider a very correct approach given the decision-making responsibility of such a Committee.

“The authors have replied with a number of points that we would like to challenge"

- *p2: "Re the suggestion of an upper safe limit of organic selenium of 20 µg/d by Vinceti et al., the authors now justify the original inclusion of that statement on the basis of a study (ORDET) based on a semi-quantitative FFQ at baseline and follow-up for development of type-2 diabetes 16 years later. Based on that same study (p4), the authors refer to "Such a diabetogenic effect of selenium….". A prospective study, especially one with a very weak study design such as ORDET, can only show an association—hardly a good basis for making such a statement in a Cochrane review. Furthermore, an upper safe limit of organic selenium of 20 µg/d would be just above that at which Keshan Disease is seen—11 mg/d in a Chinese man, which translates to 14 µg/d in a man of Western body weight.*

As written in our original response, the suggestion of a safe upper limit of 20 µg/L was based on the ORDET study results already available and published as an abstract in *Epidemiology* in 2009. Stating that the ORDET study, one of the first and most methodologically sound European prospective studies, started in the 1980s by the Italian National Cancer Institute in Milan, was 'weak' is unacceptable. Its methodological value has been largely recognised in the scientific community and in the epidemiological literature.

Our review, however, never aimed at summarising the large epidemiological and laboratory literature addressing the issue of safe upper limit of Se exposure in humans, particularly the most recent studies.

- *p2: The authors say, "The recent availability of new data about endocrine (Stranges 2007; Lippman 2009) and dermatologic (Lippman 2009) toxicity of low doses of organic selenium adds new findings which support the recommendations by the WHO group." The authors seem still not to have taken on board the fact that Lippman et al. 2009 shows no endocrine toxicity of selenium. Furthermore, the dose given—200 mg/d—was not low.*

The relation between selenium and excess diabetes risk is an extremely important issue that clearly would require extensive review, but this was not the aim of our Cochrane review;therefore we would like to refer Dr Brigelius-Flohé and colleagues to the most recent studies and reviews on the topic. It would also be useful to remind Dr Brigelius-Flohé and colleagues that the SELECT trial found an excess risk of diabetes, which understandably caused concern for its "Data and safety monitoring Committee" (see above) and contributed to the anticipated ending of the trial. We took note that Dr Brigelius-Flohé and colleagues do not consider the SELECT supplemental dose of 200 mg/Se/d to be a 'low' dose; actually, it was so high that it could be toxic.

- *p6: "We hotly dispute the assertion of the authors (none of whom is a nutritionist) that "The assessment of selenium intake, despite the difficulties associated to its variability and the possible individual variability in absorption, in some cases might even yield better estimates of actual exposure compared with biomarkers".*

Different exposure assessment methods have different advantages and disadvantages. What we stated in our review was, "A concern, which we cannot clarify to date, is that biomarkers do not adequately reflect intake of both organic and inorganic selenium species". We still think there is currently no way of clarifying this.

We were very surprised in reading comments such as 'None of the authors is a nutritionist', not just because this is incorrect (one of the review authors, MB, is an accredited and practicing dietician and nutritionist), but also for the underlying and clearly 'biased' concept: that the right to conduct independent research should be determined by subjective value judgements by one's peers.

Despite the detailed comments made by Dr Brigelius-Flohé et al regarding key statements we have made and details of the studies we have identified in preparing the review, we remain convinced that the conclusions drawn from the original version of the review remain valid: We have not demonstrated a protective effect of selenium against cancer in men, women or children.

Contributors

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Selenium for preventing cancer, October 2018

Summary

Comment: John Endicott Consumer Peer Review of January 29, 2018 Cochrane Review Selenium for Preventing Cancer Authors: Vinceti M et al.

(1) "Suboptimal systematic reviews and meta-analyses can be harmful given the major prestige and influence these types of studies have acquired." John Ioannidis, The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses, Milbank Quarterly, Vol. 94, No. 3, 2016 (emphasis added)

(2) "Indeed, research may find we would be better off to scrap peer review entirely. The readers … will continue to be the final and harshest judges." Drummond Rennie, Guarding the Guardians: A Conference on Editorial Peer Review, JAMA, November 7, 1986

(3) "What a Load of Rubbish. Scientists have lost their taste for self-policing and quality control. … The hallowed process of peer review is not all it is cracked up to be, either. … Peer review should be tightened—or perhaps dispensed with altogether, in favour of post-publication evaluation in the form of appended comments." How Science Goes Wrong, The Economist, October 19, 2013

I am posting this as an unsolicited consumer peer review Comment on the above extremely flawed Cochrane Review. I am a 'consumer' of one of the "selenium" supplements discussed in this Cochrane review, and am also a 'reader' of a number of relevant RCTs and interpretive standards which Cochrane peer reviewers have unaccountably overlooked. Accordingly, I am also a 'harsh judge' of the failure of Cochrane peer review in this instance. I do believe that "following the recommendations of [this 2018 Cochrane Review, 'Selenium for Preventing Cancer'] could result in harm to patients or populations of interest"—within the meaning of Cochrane's own publishing policy "Process in the event of serious errors in published Cochrane Reviews." (emphasis added).

Specifically, I agree with Dr. Walter Willett of Harvard University who this month (March 13, 2018) in the Journal of the American Medical Association writes that "study findings can be buried in a poorly planned meta-analysis", and I also agree with Dr. Michael Bracken of Yale University, a long-time Cochrane collaborator, when he says that he is "not going to defend" the meta-analysis of cancer mortality effects appearing on page 160 of this 2018 Cochrane review. The flawed meta-analysis on page 160 has, for the time being, "buried" an astounding finding of a 41% reduction in cancer mortality in study participants (confidence interval 0.42-0.89, P value .008).

As Cochrane co-founder Iain Chalmers pointed out only two years ago, "there is a vast potential gain from salvage operations [including] rescuing sunken trials from the bottom of the ocean … " (1). Read on, and see if you do not agree that the cancer mortality RCT in question —styled NPCT 2002 in this Cochrane 2018 "selenium" review—must be unburied from the watery grave to which Cochrane authors Vinceti et al. have seen fit to consign it.

I. To begin at the beginning: Item 1 on the March 2017 "Consumer peer-review form for a Cochrane intervention review" states "we do not expect you to comment on the title [but] please do so", if you can "suggest an improvement." Well, despite being warned off, I'm going to start by commenting on the review's title, and will suggest an improvement.

Iain Chalmers, several years before he co-founded the Cochrane Collaboration in 1992, wrote a letter to the British Medical Journal, "Proposal to outlaw the term 'negative trial'" (2). In a similar vein, I would put it to you that Cochrane should have outlawed the term "selenium" from appearing anywhere in this review, insisting instead that the authors substitute—for each of their hundreds upon hundreds of uses of "selenium" (starting of course with the first word of the review's title)—the proper term: "selenium compounds". The term "selenium" means only one thing: elemental Se, which has never been employed as an intervention in any of the 388 studies referred to by Vinceti et al. in this 2018 version of their Cochrane review. (There was an earlier 2014 version of the review by the same authors).

Advice to Cochrane: Always insist that authors employ correct terminology for an intervention—otherwise, as in this case, the consequences to consumers can be dire. Harvard's most noted living biologist E.O. Wilson insists on this point: "A great deal of the future of biology [and medicine, too] depends on the strengthening of taxonomy, for if you cannot tell one kind of plant [or therapeutic intervention] from another, you're in trouble. Some kinds of research may be held up indefinitely [as has been the case with a replication trial here, see infra]. As the Chinese say, the beginning of wisdom is getting things by their right names." (3).

Next point: the most important health outcome discussed in this 2018 review is cancer mortality. In "a recent popular survey in which people were asked how they would choose to die … 0% chose cancer." (4).

Item 9 on the 2017 Cochrane consumer peer review form asks, "Are the most important outcomes to you listed in the 'Summary of Findings' table?" This question can only be answered "No", since cancer mortality appears nowhere among the several outcomes listed in the Summary of Findings on pages 4-5 of the review.

You must go all the way to page 160 of the review to locate the "poorly planned" (Walter Willett's term, supra) meta-analysis for cancer mortality, representing Vinceti et al.'s attempt to "bury" the NPCT results which Willett long ago described as "more important than anything else we know about in cancer prevention." (5).

Dr. Michael Bracken, professor emeritus of epidemiology at Yale School of Public Health, has reacted as follows to Cochrane's meta-analysis (pooling results of NPCT 2002 and SELECT 2009, the only two studies which have reported total cancer mortality results for selenocompound intervention):

"I am not going to defend the [Cochrane] meta-analysis. An [I2 value] of >75% is usually regarded as an indication that the meta-analysis is inappropriate. Instead of calculating a summary risk estimate which is essentially meaningless in the presence of high heterogeneity, my preference would be to examine the two trials in detail to see why they give statistically different results (the confidence interval of each trial excludes the point estimate of the other)." (emphasis added) (6).

(The word "meaningless", used by Professor Bracken, comes from section 9.5.1, "What is heterogeneity?", in the Cochrane Handbook, q.v. Professor Bracken is listed in the acknowledgments for his contribution to this chapter of the Handbook).

Cochrane's 2017 "peer review checklist" asks the question, "Have sources of heterogeneity been identified?" If the designated peer reviewer(s) did in fact answer "Yes" to this item on the checklist, there is only one brief, backhanded and wrongheaded reference in the entire 236-page review to support such a "Yes" answer, as follows:

"The turning point of research on selenium and cancer was the SELECT trial (SELECT 2009) … . The intervention used in this trial was different from that used in NPCT (selenomethionine in SELECT, and selenised yeast in [NPCT]), although this is unlikely to have been

responsible for observed differences (Waters 2013); in both cases, the intervention comprised organic selenium species (Block 2004)." Cochrane 2018 "Selenium … " Review, at p. 31.

Block 2004, one of the dozens of speciation analyses of selenised yeast (SeY) published to date, refers to a number of selenium compounds other than selenomethionine (SeMet) which can be found in the nutritional supplement SeY (obtainable over the counter in any pharmacy). As analytic techniques have improved over the years, over 100 seleno compounds have now been detected in SeY. (7).

What is wanted—to support the Cochrane meta-analysis combining the extremely dichotomous results of these two studies of extremely heterogeneous interventions—is a head-to-head trial of SeY and SeMet showing that they are bioequivalent with respect to the clinical outcome of total cancer mortality.

Waters 2013, in the version cited by Vinceti et al. is unlocatable (even in abstract form) on the Internet, but is clearly identical to the November 2012 report by Waters, Shen, et al. in the journal Nutrients, describing a head-to-head (biomarker) study of the effects of SeY and SeMet—in 49 elderly beagles. The Waters study proved unable to support "the possibility that SeMet and Se-yeast are not equipotent in promoting … cancer risk reduction in the aging prostate [of beagles]." (8).

However, the 2018 Cochrane "selenium" review unaccountably overlooks a second head-to-head study comparing the effects of SeY and SeMet in humans. This 2014 study showed "reductions in ['prostate cancer relevant'] biomarkers of oxidative stress following supplementation with SeY but not [with] SeMet in healthy men." (emphases added). Comparative effects of two different forms of selenium on oxidative stress biomarkers in healthy men: a randomised clinical trial. (9). The 2018 Cochrane Review authors claim, on page 8, to have included clinicaltrials.gov in their literature search. Had they actually done so, the Richie trial would not have been hard to locate. The report of the Richie trial is among only 17 trials—all human, of course—which show up following a search for trials of "selenium" and "prostate cancer." The 2018 Cochrane Review's passing over (or suppression) of the Richie human head-to-head study showing cancer biomarker effectiveness of SeY, versus ineffectiveness of SeMet, calls to mind this observation by Ben Goldacre, in his 2012 book Bad Pharma:

"We proceed by testing things … in head-to-head trials and gathering together all of the evidence. This last step is crucial: if I withhold half the data from you, it's very easy for me to convince you of something that is not true. … [S]o every time time we fail to publish [or cite] a piece of research, we expose real, living people to unnecessary, avoidable suffering [including death]." (emphasis in original) (10).

Citing a null beagle study, while at the same time failing to cite a positive human study, is a perfect example of Goldacre's point, and is also a perfect example of John Ioannidis' larger point, supra, which I will quote again:

"Suboptimal systematic reviews and meta-analyses can be harmful given the major prestige and influence these types of studies have acquired." (emphasis added).

And while I'm criticizing the external peer reviewer(s) for not catching up Vinceti et al. for their failure to credibly explain the "sources of heterogeneity" in their highly heterogeneous meta-analysis, I feel I should call out as well the internal Cochrane peer reviewers, who appear to include: (1) an Information Specialist; (2) a Cochrane Review Group Advisor; (3) a Contact Editor; and (4) a Sign-Off Editor.

Advice to Cochrane: At least one—and probably all—of the above internal Cochrane peer reviewers should, as a matter of the most basic auditing of a Cochrane review, have read in its entirety at least one cited study for the major outcome, total cancer mortality in this case. Here, that one study report would obviously have been the $150 million RCT, Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). (11).

And in reading this SELECT report, it would be a good idea to have in mind a question such as: "I wonder if this study has anything to say about whether it considers its intervention, SeMet, to be bioequivalent to SeY, the intervention in NPCT?"

Had the Cochrane internal editors performed this uber-simple spot check, they would have found that the 33 authors of the SELECT report explicitly disclaimed any notion that their study of SeMet could be viewed as refuting in any degree the results of the NPCT study of SeY:

"[T]he formulation (high-selenium yeast) given in the NPCT trial may have been more active than the l-selenomethionine given in SELECT …. [I]t is impossible to know now whether selenized yeast would have been more active than l-selenomethionine … in SELECT." (12).

I would put it to the Cochrane editorial team that these clear statements joined in by the 33 SELECT authors are, if read and absorbed, plain red flags that should have foreclosed Vinceti et al.'s misguided pooling of the results of these two RCTs in the Cochrane total cancer mortality meta-analysis on page 160 of the 2018 review.

To sum up: SELECT is a "fair test" of SeMet. NPC is a "fair test" of SeY. And, as the SELECT authors make pellucidly clear to anyone paying attention, SELECT can in no way be viewed as a "fair test" of SeY—and so, SeY is very much still 'in play' as a potentially very effective chemopreventive agent, no reason at all not to perform a true replication trial, stat. But do not hold your breath waiting for anyone to step up to fund such a replication trial, at least not so long as the fatally flawed 2018 Cochrane "selenium" review is not withdrawn per Cochrane's own "Process in the event of serious errors in published Cochrane Reviews."

Of course, Cochrane can always first go back to Vinceti et al. and ask, “By any chance, can you cite some new evidence—better than your Waters 2013 elderly beagle study whose value (assuming it had any value in the first place) has been obliterated by the Richie 2014 human study—which could support your pooling of SELECT and NPCT cancer mortality results? If the answer is ‘Yes, we can’, by all means let’s look at this newly-found evidence.” I strongly suspect there is none, but no harm in asking for some real “evidence”, as Iain Chalmers did in 1989 at the first JAMA/BMJ conference on peer review:

“The inaugural Peer Review Congress was held in a distinctly shabby hotel in Chicago, Illinois, in 1989. It was engaging and contentious: presenters studied the demography of reviewers at various journals, how often individuals conducted reviews, blinding, statistical reporting and much more. I was thrilled to see actual data.

“A distinguished editor in the audience took another view, excoriating presentation after presentation. Finally, Iain Chalmers (who later co-founded the Cochrane Collaboration) stood and addressed him: ‘We have listened to your incessant criticisms of everyone who has gone to the trouble of obtaining data. What we have not heard from you is one single piece of evidence for your opinions.’ There was loud applause, and the future of these congresses was assured. They have taken place every four years since — in much better hotels.” Drummond Rennie, Let’s make peer review scientific, Nature, 05 July 2016, 31-33.

[Final note, on “risk of bias”: The 1/29/18 Cochrane “Selenium” Review claims to follow GRADE guidelines in assessing an alleged “risk of bias” in the NPCT 2002 SeY trial. If you look further into this claim, which is repeated over and over again in the text of the review, you will see that it applies only to a risk of overstating the results of SeY supplementation for the outcome of prostate cancer incidence (resulting from a much higher rate of biopsy in the placebo arm of the study).

But, according the GRADE guidelines, “Summarizing study limitations must be outcome specific. Sources of bias may vary across outcomes. … For instance, RCTs of steroids for acute spinal cord injury measured both all-cause mortality and, based on a detailed physical examination, motor function. Blinding of outcome assessors is irrelevant for mortality but crucial for motor function.”

Think about it: what effect would this alleged detection bias resulting in over ascertainment of prostate cancer incidence in the placebo group have on the outcome of total cancer mortality?

Isn’t it obvious—the purpose (and, indeed, the effect) of early CaP detection being to reduce cancer mortality—that the alleged detection bias actually favours SeY treatment for the mortality outcome? In other words, the alleged bias runs in two different directions for these two outcomes. As the Cochrane Risk of Bias Tool 2.0 states: “If the likely direction of the bias [for a particular outcome] can be predicted, it is helpful to predict this.” This flawed 2018 Cochrane review being such a shoddy product, it should come as no surprised to anyone that this extremely important point, along with many others, was overlooked entirely by the review authors, (and not picked up by the Cochrane peer reviewers, either, of course).

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Reply

We wish to thank Dr. Endicott for his comments. In response, we have amended the text of the review with reference to the following points:

a) Title. It was suggested that we change “selenium” to “selenium compounds” in the title and elsewhere. We acknowledge the relevance of the issue, and point out that the issue and importance of selenium speciation has been extensively considered throughout the current version of the review. We think that readers are unlikely to be misled into thinking that the review pertains exclusively to elemental selenium. Therefore we have not been asked by the Cochrane Editorial Methods Department to modify the original title of this Cochrane review, which has been unchanged since its original 2005 protocol.

b) Cancer mortality (and incidence). For the GRADE assessment and the related summary of findings, we were originally limited to seven outcomes, which have now been extended to eight. We have now added to the two summary of findings tables a) mortality from all cancer from experimental studies (RCTs) at low risk of bias, and b) mortality from all cancer from non-experimental (observational) studies. Both estimates were already reported in the abstract.

c) NPC-SELECT pooling. According to the methodology we have adopted for the entire assessment and all outcomes, i.e., to focus on randomised controlled trials and particularly on those at low risk of bias, we have not pooled NPC and SELECT for these additional outcomes reported in the GRADE assessment, due to their different risk of bias (possibly due to a breaking of blinding in the former, and for which the authors acknowledged a severe detection bias with reference to prostate biopsy rate). We have also extensively mentioned in the review how experimental human studies differed in term of selenium compounds administered, as well as how non-experimental studies lacked exposure assessment of single selenium species. Both these issues may have been potential source of heterogeneity, as highlighted in the review.

d) The 2014 Richie et al. study and the Waters 2013 study. We now mentioned Richie et al. 2014 (as well as the comparable Rav-Haren et al. Br J Nutr 2008 trial) which, though not eligible for our review, may be of help in showing how the proteomic and toxicological effects of the various selenium compounds administered to humans can be complex and inconsistent. These issues are definitively of interest to the relation between selenium and cancer risk. With reference to our Waters 2013 citation, we added more detail in the reference, to better allow readers to locate it.

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Contributors

Marco Vinceti and Tommaso Filippini on behalf of the auhtor team.

WHAT'S NEW

Date	Event	Description
27 February 2020	Amended	Minor edit to text made.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 5, 2011

Date	Event	Description
12 November 2018	Amended	Minor edits made in relation to feedback submitted.
12 November 2018	Feedback has been incorporated	Feeback and author's response added.
18 January 2018	New citation required but conclusions have not changed	Addition of some recent references and minor edits.
8 February 2017	New search has been performed	New literature search conducted 8 February 2017.
3 February 2015	Feedback has been incorporated	Feedback and trial author's response added
18 March 2014	New citation required but conclusions have not changed	New trials added. Meta-analysis of data from RCTs applied when at least 2 studies were available for each outcome
15 February 2013	New search has been performed	Search strategy updated
14 August 2012	Feedback has been incorporated	Additional feedback and trial author's response incorporated
8 March 2012	Feedback has been incorporated	Feedback submitted and trial author's reply added

CONTRIBUTIONS OF AUTHORS

1. MV co-ordinated the current update, commented on the protocol and the review, screened search results, appraised study bias, and updated the draft in collaboration with the other review authors.
2. TF and CDG extracted data from the added papers, appraised study bias, conducted data analyses, commented on the review, wrote part of the draft, and provided a methodological perspective.
3. CDG commented on the review, appraised study bias, prepared the 'Summary of findings' (GRADE) tables, wrote part of the draft, and provided a methodological perspective.
4. GD is the primary author of the first version of the review and was involved in all steps of the present update, including commenting on the protocol and the manuscript, extracting data from papers, and providing a methodological perspective.
5. MZw commented on the protocol and the review and provided a methodological perspective.
6. MB commented on the protocol and provided feedback at various stages of the review.
7. MZe commented on the protocol and the review and provided feedback on different portions of these documents.
8. MH commented on the protocol, extracted data from papers, and commented on the review text at various stages of the review.
9. RDA commented on the protocol and provided feedback at various stages of the review.
10. CMC commented on the protocol and on the review, wrote part of the draft, and provided a methodological perspective.

All review authors have reviewed and approved the final draft of this update.

DECLARATIONS OF INTEREST

1. MV: none known.
2. TF: none known.
3. CDG: none known.
4. GD: none known.
5. MZw: none known.
6. MB: none known.
7. MZe: Maurice Zeegers is the first investigator and the coauthor of included observational and experimental studies.
8. MH: none known.
9. RDA: none known.
10. CMC: none known.

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- Fondazione Pietro Manodori (Reggio Emilia), Italy, Other.

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- Fondazione di Vignola, Italy.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the previous Cochrane review, review authors adapted the risk of bias assessment for RCTs, which was introduced by Cochrane after publication of our protocol; we used the Jadad score and the Delphi list to assess the quality of RCTs, but because the results of these checklist assessments were of no relevance for this review, we have omitted them.

With respect to the protocol, in this second updated review (as well as in the previous update), we decided to perform meta-analysis of RCTs when at least two studies were available, and to emphasise the analysis conducted for all RCTs and for RCTs at low risk of bias, to highlight the most reliable and recent evidence on the selenium and cancer relation, which comes from well-designed experimental studies. As in the previous version of the review, we included in our analysis both primary and secondary outcomes of RCTs, as well as adverse effects reported in these studies. Furthermore, we updated the methods section to clarify that the main ‘primary’ analysis included analyses examining low risk of bias trials only, and ‘sensitivity analyses’ consisted of analyses that included all trials, regardless of risk of bias.

In this update, we included a 'Summary of findings' table for RCTs with low risk of bias, and one for observational studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Case-Control Studies; Neoplasms [*prevention & control]; Observational Studies as Topic; Odds Ratio; Randomized Controlled Trials as Topic; Selenium [*administration & dosage] [adverse effects]; Sex Factors; Trace Elements [*administration & dosage] [adverse effects]

MeSH check words

Female; Humans; Male